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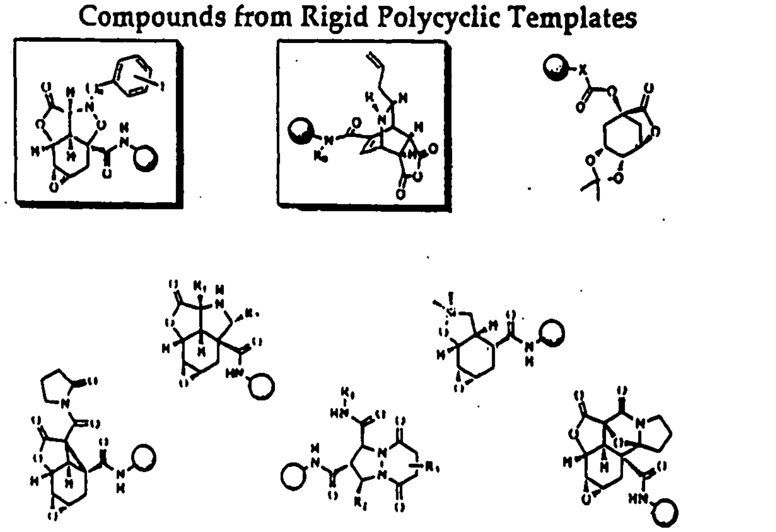
(54) Title: SYNTHESIS OF COMBINATORIAL LIBRARIES OF COMPOUNDS REMINISCENT OF NATURAL PRODUCTS

(57) Abstract

The present invention provides complex compounds reminiscent of natural products and libraries thereof, as well as methods for their production. The inventive compounds and libraries of compounds are reminiscent of natural products in that they contain one or more stereocenters, and a high density and diversity of functionality. In general, the inventive libraries are synthesized from diversifiable scaffold structures, which are synthesized from readily available or easily synthesizable template structures. In certain embodiments, the inventive compounds and libraries are generated from diversifiable scaffolds synthesized from a shikimic acid based epoxyol template. In other embodiments, the inventive compounds and libraries are generated from diversifiable scaffolds synthesized from the pyridine-based template isonicotinamide. The present invention also provides a novel ortho-nitrobenzyl photolinker and a method for its synthesis. Furthermore, the present invention provides methods and kits for determining one or more bi logical activities of members of the inventive libraries. Additionally, the present inventi n provides pharmaceutical compositi ns containing one or more library members.

Stereoselective Synthesis of Natural Product-Like Compounds from Rigid Polycyclic Templates



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SYNTHESIS OF COMBINATORIAL LIBRARIES OF COMPOUNDS REMINISCENT OF NATURAL PRODUCTS

Related Applications

The present application claims priority to US application number 09/121,922 entitled "Synthesis of Combinatorial Libraries of Compounds Reminiscent of Natural Products" filed July 25, 1998, which is a continuation-in-part of co-pending application number 08/951,930, filed October 15, 1997, entitled "Droplet Assay System", which in turn claims priority to provisional application 60/049,864 entitled "Droplet Assay System" filed June 6, 1997. The entire contents of each of these applications are incorporated herein by reference.

Background of the Invention

The identification of small organic molecules that affect specific biological functions is an endeavor that impacts both biology and medicine. Such molecules are useful as therapeutic agents and as probes of biological function. For example, progress in whole genome sequencing (see, for example, Collins, F.S.; Patrinos, A.; Jordan, E.; Chakravarti, A.; Gesteland, R.; Walters, L.; and the members of the DOE and NIH planning groups *Science* **1998**, *282*, 682) has facilitated a related method of exploring biological systems. The sequencing of, for example, the estimated 80,000 to 100,000 genes in the human genome is uncovering a myriad of novel genes with unknown functions. In the "reverse genetic" approach, a deletion, or "knockout" mutation is targeted to a known gene of unknown function. This is followed by a broad search for all resulting biological effects, allowing the function of the gene to be inferred. In but one example from the emerging field of chemical genetics, in which small molecules can be used to alter the function of biological molecules to which they bind, these molecules have been effective at elucidating signal transduction pathways by acting as chemical protein knockouts, thereby causing a loss of protein function. (Schreiber et al. *J. Am. Chem. Soc.* **1990**, *112*, 5583; Mitchison, *Chem. and Biol.* **1994**, *1*, 3) Additionally, due to the interaction of these small molecules with particular biological targets and their ability to affect specific biological functions, they may also serve as candidates for the development of therapeutics.

Because it is difficult to predict which small molecules will interact with a biological target, intense efforts have been directed towards the generation of large numbers, or "libraries", of small organic compounds. These libraries can then be linked to sensitive screens to identify the active molecules. In many cases, researchers have developed "biased" libraries, in which all members share a particular characteristic, such as an ability to interact with a particular target

ligand, or a characteristic structural feature designed to mimic a particular aspect of a class of natural compounds. For example, a number of libraries have been designed to mimic one or more features of natural peptides. Such "peptidomimetic" libraries include phthalimido libraries (WO 97/22594), thiophene libraries (WO 97/40034), benzodiazopene libraries (US 5, 288, 514), libraries formed by the sequential reaction of dienes (WO 96/03424), thiazolidinone libraries, libraries of metathiazanones and their derivatives (US 5, 549, 974), and azatide libraries (WO 97/35199) (for review of peptidomimetic technologies, see Gante, J., *Angew. Chem. Int. Ed. Engl.* 1994, *33*, 1699-1720 and references cited therein).

Each of these libraries has provided solid phase synthetic strategies for compounds possessing specific core functionalities, but none achieves the complexity of structure found in natural products, or in other lead compounds prepared through traditional chemical synthetic routes. Complex natural products commonly contain several different functionalities and often are rich in stereochemical complexity. Such diversity and complexity are difficult to achieve if the synthesis is restricted to a specific class of compounds.

Recognizing the need for development of synthetic strategies that produce large numbers of complex molecules, Boger et al. (EP 0774 464) have recently developed a solution-phase synthetic strategy for producing a library of compounds based on a functionalizable template core, to which various reagents can be added.

However, there remains a need for development of solid-phase strategies, where the more rapid production methods such as split-and-pool strategies can be employed to generate larger (> 1,000,000), more complex, preferably natural product-like, libraries. Additional solution-phase strategies would, of course, also be valuable.

Summary of the Invention

The present invention provides methods for the production of compounds and libraries of complex compounds reminiscent of natural products from diversifiable scaffold structures. In particular, the present invention provides synthetic strategies that allow production of complex compounds and preferably large collections of complex compounds that are reminiscent of natural products in that they contain one or more stereocenters, and a high density and diversity of functionality. In preferred embodiments, the compounds of the present inventive libraries are structurally related to a natural product. Alternatively or additionally, the compounds of the inventive libraries possess the capability of acting as a ligand in a biological system to produce a desired inhibitory or promoter effect, and thus may also be functionally reminiscent of natural products.

According to the present invention, the inventive compounds and combinatorial libraries are synthesized from diversifiable solid support bound scaffolds, which are synthesized from readily available or easily synthesizable template structures. In certain embodiments, the inventive compounds and libraries are generated from diversifiable scaffolds synthesized from a shikimic acid based epoxyol template. In other embodiments, the inventive compounds and libraries are generated from diversifiable scaffolds synthesized from the pyridine-based template isonicotinamide.

In addition to providing complex compounds reminiscent of natural products, combinatorial libraries thereof, and methods of their production, the present invention also provides a novel ortho-nitrobenzyl photolinker, and a method for its synthesis, that can be used in the preparation of solid suppport bound compounds and combinatorial libraries.

The present invention further provides a method for determining one or more biological activities of a library member. In a preferred embodiment, the method for determining one or more biological activities of the inventive compounds comprises contacting the inventive compounds with a biological target, such as a binding target or transcription based assay, and determining a statistically significant change in a biochemical activity relative to the level of biochemical activity in the absence of the compound.

The present invention further provides a kit comprising a library of compounds and reagents for determining one or more biological activities of the library member. To give but one example, the biological activity can be determined by providing a kit containing a binding reagent, such as a direct reagent (binding target) or an indirect reagent (transcription based assay) and a library of compounds.

The present invention additionally provides pharmaceutical compositions containing one or more library members. In a preferred embodiment, the pharmaceutical composition preferably comprises one or more of the inventive compounds and a pharmaceutically acceptable carrier.

Definitions

"Combinatorial library": As used herein, a "combinatorial library" is a plurality of complex compounds reminiscent of natural products synthesized from diversifiable scaffold structures by employing different reactants, or monomers, at each stage of the diversification of the scaffold structures. The combinatorial libraries of the present invention may be prepared in solution or on the solid phase.

"Diversifiable scaffold structures": As used herein, a "diversifiable scaffold structure" is a compound synthesized from a template structure, which contains unique latent or active

functionalities capable of being further reacted with synthetic reagents to generate at least one new functionality, but, particularly in the case of a latent functionality, may generate more than one. As used herein, a "latent functionality" is one that is present, but is temporarily inactive. Upon release with an activator or reagent, the latent functionality becomes active, and is thus available for further diversification. For example, a diversifiable scaffold structure may contain an epoxide moiety, which, upon reaction with a nucleophile releases a latent alcohol functionality and generates an additional functionality at the site of nucleophilic attack. Furthermore, the alcohol functionality can be subseqently diversified using electrophiles to yield other functionalities including, but not limited to, ether, ester, carbamate and thioester.

"Complex compounds reminiscent of natural products": As used herein, a complex compound reminiscent of a natural product is a compound that, similarly to complex natural products which nature has selected through evolution, contains more than one stereocenter, a high density and diversity of functionality, and a diverse range of atoms within one structure. This term can also, for the purposes of the present invention, be used interchangeably with the term "natural product-like" compound. In this context, diversity of functionality can be defined as varying the topology, charge, size, hydrophilicity, hydrophobicity, and reactivity, to name a few, of the functional groups present in the compounds. The term, "high density of functionality", as used herein, can preferably be used to define any molecule that contains at least four latent or active diversifiable functional moieties. These structural characterisitics may additionally render the inventive compounds functionally reminiscent of complex natural products, in that they may interact specifically with a particular biological receptor, and thus may also be functionally natural product-like.

"Small Molecule": As used herein, the term "small molecule" refers to an organic compound either synthesized in the laboratory or found in nature. Typically, a small molecule is characterized in that it contains several carbon-carbon bonds, and has a molecular weight of less than 1500, although this characterization is not intended to be limiting for the purposes of the present invention. Examples of "small molecules" that occur in nature include, but are not limited to, taxol, dynemicin, and rapamycin. Examples of "small molecules" that are synthesized in the laboratory include, but are not limited to, the inventive compounds incorporated herein.

"Linker": The term "linker", as used herein, refers to a molecule or group of molecules connecting a solid support and a combinatorial library member. The linker may be comprised of a single linking molecule or may comprise a linking molecule and a spacer molecule, intended to separate the linking molecule and the library member by a specific distance.

"Radially Arrayed": The term "radially arrayed" as used herein, refers to a spatial arrangement of functionality that projects outwardly in all directions, from the synthesized scaffold structure.

"Protecting Group": The term "protecting group" as used herein, refers to a chemical group that reacts selectively with a desired fuctionality in good yield to give a derivative that is stable to further reactions for which protection is desired, can be selectively removed from the particular functionality that it protects to yield the desired fuctionality, and is removable in good yield by reagents compatible with the other functional group(s) generated during the reactions.

"Support": The term "support", as used herein interchangeably as beads, solid surfaces, substrates, particles, supports, etc. These terms are intended to include 1) solid supports such as beads, pellets, disks, capillaries, pore-glass beads, silica gels, polystyrene beads optionally cross-linked with divinylbenzene, grafted co-poly beads, poly-acrylamide beads, latex beads, dimethylacrylamide beads optionally cross-linked with N, N'-bis acryloyl ethylene diamine, glass particles coated with a hydrophobic polymer, or any other material having a rigid or semi-rigid surface; and 2) soluble supports such as low molecular weight non-cross-linked polystyrene. These materials also contain functionalities such that identifiers and/or templates, scaffolds, and inventive compounds can be attached to them. It is particularly preferred for the purposes of the present invention that the solid support Tentagel is used.

"Identifier Tag": The term "identifier tag" as used herein, refers to a means for recording a step in a series of reactions used in the synthesis of a chemical library. For the purposes of this application, the terms encoded chemical library and tagged chemical library both refer to libraries containing a means for recording each step in the reaction sequence for the synthesis of the chemical library.

Description of the Drawing

Figure 1 depicts several examples of natural product-like compounds.

Figure 2 depicts the diverse reaction products of one embodiment of the inventive method.

Figure 3 depicts the use of a small molecule to bind the Human Growth Hormone receptor.

Figure 4 depicts the inventive method for the shikimic acid based combinatorial library.

Figure 5 depicts the synthesis of different enantiomers of the epoxyol templates.

Figure 6 depicts the synthesis of an isonicotinamide template.

Figure 7 depicts the use of a preferred Tentagel amino resin.

Figure 8 depicts the use of a photocleavable linker to attach the solid phase resin to the desired template structure.

Figure 9 depicts the synthesis of a novel ortho-nitrobenzyl photolabile linker.

Figure 10 depicts alternative ortho-nitrobenzyl photolinkers.

Figure 11 depicts a dithiane-protected benzoin photolinker.

Figure 12 depicts addition of a diversity position via Fukuyama sulfonamide alkylation.

Figure 13 depicts the synthesis and tandem reaction of the nitrone portion.

Figure 14 depicts the synthesis of iodophenyl nitrones.

Figure 15 depicts the synthesis of alternative scaffold structures.

Figure 16 depicts acetoacetate as a synthetic intermediate.

Figure 17 depicts the solid phase synthesis of rigid polycyclic core structures.

Figure 18 depicts the synthesis of isoquinuclidine scaffolds.

Figure 19 depicts the asymmetric synthesis of 1,2-dihydropyridines.

Figure 20 depicts the use of a sugar based chiral auxiliary.

Figure 21 depicts a novel rearrangement from photolytic cleavage.

Figure 22 depicts examples of solid phase cycloaddition chemistry.

Figure 23 depicts further reactions of isoquinuclidine scaffolds.

Figure 24 depicts solution phase lactone aminolysis.

Figure 25 depicts aminolysis of the tetracycle with n-butylamine.

Figure 26 depicts 2-hydroxypyridine-catalyzed butyrolactone aminolysis.

Figure 27 depicts acylation of the unmasked hydroxyamide.

Figure 28 depicts epoxide ring opening reactions.

Figure 29 depicts additional epoxide ring opening reactions.

Figure 30 depicts chemoselective solvolysis with AcSH and AcOH.

Figure 31 depicts epoxide thiolysis.

Figure 32 depicts solid phase palladium chemistry.

Figure 33 depicts examples of palladium cross-coupling reactions at the aryl iodide.

Figure 34 depicts rhodium-catalyzed hydroacylation and azide cycloaddition at the aryl alkyne.

Figure 35 depicts nitrone and nitrile oxide, alkyne cycloadditions.

Figure 36 depicts representative potential nucleation points of the isoquinuclidine scaffold.

Figure 37 depicts the efficient synthesis of N-arylimide derivatives.

Figure 38 depicts representative diversity sites for the cup-like pentacyclic scaffold.

Figure 39 depicts a synthetic plan for the geneation of 46.5 million complex molecules.

Figure 40 depicts a synthetic plan for the generation of 30 million complex molecules.

Figure 41 depicts a test library synthesis library quality control.

Figure 42 depicts monomer screening.

Figure 43 depicts library quality control for a small test library.

Figure 44 depicts demonstration compounds.

Figure 45 depicts the synthesis of a test library of isoquinuclidine-based compounds.

Figure 46 depicts the use of photorelease of the inventive compounds into nanodroplets.

Figure 47 depicts the ability of the shikimic acid test library to activate the 3TP promoter.

Figure 48 depicts the antagonism of TGF-β-induced reporter gene activity.

Figure 49 depicts the inhibition of mink lung cell growth by the test library.

Figure 50 depicts the ability of KC233 to arrest mink lung cells in the S-phase of the cell cycle.

Figure 51 depicts fully elaborated products 42a-f.

Figure 52 depicts testing of potential building blocks for the shikimic acid-based library.

Figure 53 depicts alkyne building blocks.

Figure 54 depicts amine building blocks.

Figure 55 depicts carboxylic acid building blocks.

Figure 56 depicts representative LC-MS data for testing of building blocks.

Figure 57 depicts tetracycle and building blocks used in the test library.

Figure 58 depicts alkyne and amine building block masses and the resulting 64 unique γ-hydroxyamide product masses.

Figure 59 depicts respresentative LC-MS data for test library pool 43{X,X,4} acylated with Acid 4.

Figure 60 depicts the coupling of Still's polyhaloaromatic EC-GC tags directly to the polystyrene backbone of beads using mild carbene insertion chemistry.

Figure 61 depicts results for a mink lung cell proliferation assay.

Figure 62 depicts activators of the TGF-β-responsive reporter gene.

Figure 63 depicts results for TGF-β-responsive reporter gene assay.

Figure 64 depicts results for TGF-β-reponsive reporter gene assay.

Figure 65 depicts numbered acid building blocks tested.

Figure 66 depicts numbered amine building blocks tested.

Figure 67 depicts numbered alkyne building blocks tested.

Figure 68 depicts representative EC-GC trace for binary encoding tag analysis.

Description of Certain Preferred Embodiments

As described herein, the present invention provides complex radially arrayed compounds and libraries of compounds, and methods for making such libraries. In general, the present invention provides synthetic strategies that allow production of compounds and large collections of compounds that are reminiscent of complex natural products in that they contain at least one stereocenter, a high density and diversity of functionality displayed in a radial array, and a diverse range of atoms within one structure. In this context, diversity of functionality can be defined as varying a specific characteristic or set of characteristics of the functional groups present in the molecule including, but not limited to, topology, size, charge, hydrophilicity, hydrophobicity, and reactivity. Examples of ways in which functional groups may differ from one another include, but are not limited to, variations in either the shape or chain length of a particular collection of atoms or variations in the particular atoms present in the functional groups. Additionally, functional groups may also differ from one another by variations in both the shape or chain length and variations in the particular atoms present in the functional groups. In the context of the present invention, a high density of functionality can be defined as a large number of chemical moieties present in an inventive compound or library member. In preferred embodiments the inventive compounds and library members contain at least four chemical moieties. For example, in a preferred embodiment, an inventive compound or library member may contain substituted aryl, epoxide, amine and ester functionalities, and will contain at least one stereocenter. Figure 1 depicts examples of inventive compounds containing stereochemical complexity and a high density and diversity of functionality, qualities that render them reminiscent of natural products (examples include, but are not limited to, trapoxin, Taxol™, (+)-discodermolide, or rapamycin) or "natural product-like". Figure 2 depicts examples of some of the inventive compounds. Furthermore, as discussed previously, the functionality is displayed in a radial array, which, unlike many polymers or chains of peptides or other molecules, enables diversification in all directions, thus adding to the complexity of the inventive compounds and providing them with a greater likelihood of interacting with biological molecules. In certain embodiments, this complexity is achieved by designing the inventive compounds and libraries of compounds based on an existing natural product, such as ibogamine or catharanthine, or based on a receptor for a particular protein, such as the "hot spot" of human growth hormone (Figure 3). In other embodiments, the present invention also provides compounds and libraries of compounds that, although not based on an existing natual product, are reminiscent of natural products because of their stereochemical and functional complexity and diversity, and thus may be thought of as "non-natural" natural products. Whether the compounds are "non-natural" or

are based on an existing natural product, the compounds and libraries of compounds are expected to be useful as therapeutics and biological probes because of their ability to interact with biomolecules, such as proteins, carbohydrates, and nucleic acids.

In particular, the inventive method involves the synthesis of combinatorial libraries from solution phase or solid support bound scaffolds, which are synthesized from readily available or easily synthesizable template structures. The synthesis of the scaffolds and combinatorial libraries from solid support bound templates is particularly preferred because of the ease with which large numbers (> 1,000,000) of compounds can be synthesized. The template structures are preferably selected for the inventive method because they are easily synthesizable or readily available, they contain multiple reactive sites where individual combinatorial units can be added to generate scaffold structures in preferably four steps or fewer, and possess the potential for stereochemical diversity. The resulting scaffold structures are characterized by their rigidity, stereochemical and functional group complexity, high density and diversity of functionality radially arrayed (e.g., at least four functionalizable sites) from which to generate highly diversified libraries, and by the minimal need to employ protecting groups (e.g., no more than one functionality in the molecule contains a protecting group, or in the case of certain scaffold structures, no protecting groups need be employed) during the synthesis of the scaffold structures and combinatorial libraries. Preferred template and scaffold structures also include those that are capable of reacting with reagents without the need for a catalyst. Importantly, the diversity of these highly complex compounds and libraries of compounds reminiscent of natural products, as discussed above, results both from the ability to diversify the templates and combinatorializable units used to synthesize the scaffold structures, and from the diversity generated upon reaction with the latent and non-latent functionalities in the scaffold structure. This diversity, as discussed above, results from the changing of the shape, size, hydrophilicity, hydrophobicity, charge and reactivity to name a few, when introducing new functionality. In the method of the presently claimed invention, solution phase or solid phase techniques may be employed to generate combinatorial libraries containing as many as or more than one million members of complex radially arrayed compounds reminiscent of natural products, and more preferably libraries containing as many as or more than two million members of complex compounds reminiscent of natural products.

Particularly preferred embodiments of the present invention include the synthesis of compounds and libraries of compounds starting from a shikimic acid based epoxyol template and the synthesis of compounds and libraries of compounds starting from a pyridine based template, isonicotinamide. Figure 4 depicts the inventive method for the shikimic acid based

combinatorial library, in which the boxed regions depict the potential diversity nucleation points. Each chemical step thus performed in the inventive method will deliver a new monomer while concurrently generating a new position for functionality.

Various characteristics of the templates and resulting scaffolds and reactions utilized in certain preferred embodiments of the present invention are discussed in more detail below; certain examples of inventive reactions and compounds are also presented.

Synthesis of Template Structures

In one particularly preferred embodiment, the present invention provides a method for the synthesis of complex compounds and combinatorial libraries generated from scaffold structures that are synthesized from shikimic acid based epoxyol templates. In another particularly preferred embodiment, the present invention provides a method for the synthesis of complex compounds and combinatorial libraries generated from scaffold structures synthesized from a readily available isonicotinamide template. These epoxyol and isonicotinamide templates are subjected to different reaction conditions to yield different highly complex diversifiable scaffold structures from which the complex compounds and libraries of the present invention are generated.

As discussed above, the epoxyol and isonicotinamide templates are selected for the inventive method because they are easily synthesizable or readily available, contain multiple reactive sites from which to synthesize complex diversifiable structures in a minimal number of steps, preferably four steps or fewer, and possess the potential for stereochemical diversity. As will be appreciated by one of ordinary skill in the art, the method of the present invention is intended to encompass all possible stereoisomers and diastereomers for each of the reaction conditions employed.

In one particularly preferred embodiment, the synthesis of desired epoxyol templates is achieved from the natural product (-)-shikimic acid (McGowan et al. *J. Org. Chem.* **1981**, *46*, 2381; Wood et al. *J. Am. Chem. Soc.* **1990**, *112*, 8907; Mitsunobu, O. *Synthesis* **1981**, 1-28). Additionally, employing different reaction conditions in the presence of methyl shikimate enables the synthesis of enantiomers of the desired epoxyol templates as shown in Figure 5. For example, reaction under Berchtold reaction conditions, subsequent reaction with DEAD (diethylazo dicarboxylate), triphenylphosphine and benzoic acid, and reaction with LiOH yields the R, S, S acid. The other enantiomer is readily synthesized using acetoxyisobutyryl bromide, subsequent epoxidation with $NaOCH_3$ and Payne rearrangement, and finally reaction with LiOH

to yield the S, R, R acid. These epoxyol templates can be utilized for further reaction in solution, or may subsequently be attached to a solid support.

In another particularly preferred embodiment, an isonicotinamide template is easily synthesized from the commercially available reagent isonicotinoyl chloride and an amine. The use of isonicotinoyl chloride as a starting material is preferred because it provides a handle for solid phase attachment, if desired, and also because it blocks the 4-position in a tandem reaction as shown in Figure 6 (Yamaguchi et al. *J. Org. Chem.* **1985**, *50*, 287; Yamaguchi et al. *J. Org. Chem.* **1988**, *53*, 3507). In yet another particulary preferred embodiment, an alternative isonicotinamide template is synthesized via Fukuyama sulfonamide alkylation, in which a diversifiable amide functionality is created by alkylation of the nitrogen under Mitsunobu conditions. Nitrobenzenesulfonylchloride is reacted with a solid support to generate a solid support-bound sulfonamide. Subsequent reaction with triphenylphosphine or tributylphosphine and DEAD or TMAD generates a solid support bound sulfonamide containing a diversity position. Subsequent cleavage of the sulfonamide with thiophenylate, or more generally a thiophenoxide, wherein the counterion includes, but is not limited to, sodium, potassium, cesium or amine bases, wherein said amine bases include, but are not limited to, DBU, MTBD, DIPEA, or triethylamine, yields a functionalized moiety available for further reaction with isonicotinoyl chloride to yield the functionalized isonicotinamide template. In preferred embodiments, the diversifiable functionality present on the nitrogen includes but is not limited to branched or unbranched, substituted or unsubstituted alkyl, aryl, and arylalkyl moieties.

Once the synthesis of either a desired solution phase or solid support bound template has been completed, the template is then available for further reaction to yield the desired solution phase or solid support bound scaffold structure. The use of solid support bound templates is particularly preferred because it enables the use of more rapid split and pool techniques to generate libraries containing as many as or more than 1,000,000 members.

A solid support, for the purposes of this invention, is defined as an insoluble material to which compounds are attached during a synthesis sequence. The use of a solid support is advantageous for the synthesis of libraries because the isolation of support-bound reaction products can be accomplished simply by washing away reagents from the support-bound material and therefore the reaction can be driven to completion by the use of excess reagents. Additionally, the use of a solid support also enables the use of specific encoding techniques to "track" the identity of the inventive compounds in the library. A solid support can be any material which is an insoluble matrix and can have a rigid or semi-rigid surface. Exemplary solid supports include but are not limited to pellets, disks, capillaries, hollow fibers, needles,

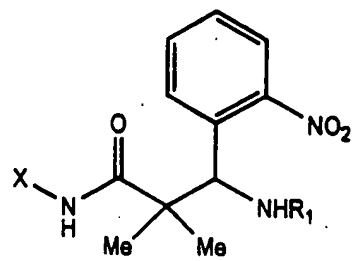
pins, solid fibers, cellulose beads, pore-glass beads, silica gels, polystyrene beads optionally cross-linked with divinylbenzene, grafted co-poly beads, poly-acyrlamide beads, latex beads, dimethylacrylamide beads optionally crosslinked with N-N'-bis-acryloylethylenediamine, and glass particles coated with a hydrophobic polymer. One of ordinary skill in the art will realize that the choice of a particular solid support will be limited by the compatibility of the support with the reaction chemistry being utilized. In one particularly preferred embodiment, a Tentagel (see, Rapp Polymere Home Page. http://www.rapp-polymere.com (accessed June 1999) amino resin, a composite of 1) a polystyrene bead crosslinked with a divinylbenzene and 2) PEG (polyethylene glycol), is employed for use in the present invention, as shown in Figure 7. Tentagel is a particulary useful solid support because it provides a versatile support for use in on-bead or off-bead assays, and it also undergoes excellent swelling in solvents ranging from toluene to water.

The compounds of the present invention may be attached directly to the solid support or may be attached to the solid support through a linking reagent, as shown in Figure 7. Direct attachment to the solid support may be useful if it is desired not to detach the library member from the solid support. For example, for direct on-bead analysis of biological activity or analysis of the compound structure, a stronger interaction between the library member and the solid support may be desirable. Alternatively, the use of a linking reagent may be useful if more facile cleavage of the inventive library members from the solid support is desired.

Furthermore, any linking reagent used in the present invention may comprise a single linking molecule, or alternatively may comprise a linking molecule and one or more spacer molecules, as depicted in Figure 7. A spacer molecule is particularly useful when the particular reaction conditions require that the linking molecule be separated from the library member, or if additional distance between the solid support/linking unit and the library member is desired. In one particularly preferred embodiment, photocleavable linkers are employed to attach the solid phase resin to the desired template structure, as shown in Figure 8. Photocleavable linkers are particularly advantageous for the presently claimed invention because of the ability to use these linkers in in vivo screening strategies. Once the template is released from the solid support via photocleavage, the complex small molecule is able to enter the cell.

In addition to providing for the synthesis of scaffold structures, compounds and libraries of compounds, in another aspect, the present invention provides a novel ortho-nitrobenzyl photolabile linker (3-amino-3-(2'-nitrophenyl)-2,2-dimethylpropionic acid (I) and a method for the synthesis of the photolabile linker, as shown in Figure 9. As shown in Figure 9, the imine (1) is synthesized in two steps from commercially available 2-nitrobenzaldehyde by modification of

a published procedure. (Kanazawa, A.M. et al., *J. Org. Chem.* **1994**, *59*, 1238) The amino ester (2) is then formed by the addition of a pre-cooled solution of (1) to the lithium enolate of methyl isobutyrate. Subsequent recrystallization from 40:60 ether/petroleum ether, hydrolysis of the synthesized ester with lithium hydroxide (LiOH), and coupling toTentagel S NH_2 using HATU yields the support bound linker (4). Importantly, this linker is incapable of β-elimination, a common decomposition pathway for photolinkers, and is stable to acid, base, and Lewis acid/amine conditions.



(I)

Referring to (I), R_1 includes, but is not limited to a protecting group, a complex compound reminiscent of a natural product, a spacer, a biomolecule, or a polymer; and X is a solid support unit.

In other particulary preferred embodiments, alternative ortho-Nitrobenzyl photolinkers are employed, such as the Rich Linker (Nba), Geysen Linker (Anp) (see, Brown et al. *Mol. Div.* **1995**, *1*, 4), Linker (A), and Affymax Linkers (Hep, Hmp, Aep) as shown in Figure 10. Additionally, a dithiane-protected benzoin photolinker, as shown in Figure 11 may be employed. One of ordinary skill in the art will also realize that any of these photolinkers as well as other photolinkers can be employed with the limitation that they will not degrade in the presence of the complex reaction steps employed in the synthesis of the compounds and combinatorial libraries. Furthermore, the method of the present invention is not limited to the use of photocleavable linkers; rather other linkers may be employed, preferably those that are capable of delivering the desired compounds in vivo.

Furthermore, as mentioned above, it may also be desirable, or even necessary, to utilize a spacer unit, to ensure that the photolinker is sufficiently distanced from the desired compound. Representative spacer units include but are not limited to aminocaproic acid (Aca), glycine, and any amino acid that does not contain a functionality capable of being acylated.

In certain embodiments, the completed template may be attached to the solid phase, through a linking unit, or directly, and subsequently used in the synthesis of desired scaffold structures. In particularly preferred embodiments, attachment of the completed templates of the present invention to the solid phase is achieved by reaction under standard amide coupling conditions. In one example, Figure 5 depicts the attachment of completed epoxyol templates to the solid phase by reaction with PyBOP, Hunig's Base and NMP, to yield a support bound epoxyol template. One of ordinary skill in the art will realize that attachment of templates to the solid phase may also be effected through alternative means, such as, but not limited to, ether linkages. This choice of linkage will depend upon the reactivity of the functionalities available in the compounds and the solid support units (including any combination of a solid support, and linking reagent) and the stability of these linkages.

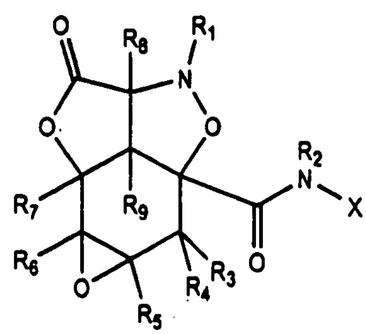
In other embodiments, one of the reagents used in the synthesis of the desired template may be attached to the solid support and the template synthesis completed while on the solid support. For example, as shown in Figure 6, attachment of isonicotinoyl chloride to the solid phase to yield a support bound isonicotinamide, is achieved by reaction with Anp-Tgl and DIPEA. Furthermore, as shown in Figure 12, alkylation of the nitrogen via Fukuyama sulfonamide alkylation, wherein nitrobenzenesulfonylchloride is reacted with a solid support to generate a solid support-bound sulfonamide, and subsequent reaction with triphenylphosphine or tributylphosphine and DEAD or TMA, generates a solid support bound sulfonamide containing a diversity position (see, Fukuyama et al. *Tet. Lett.* **1995**, *36*, 6373). Subsequent cleavage of the sulfonamide with thiophenylate, or more generally thiophenoxide, wherein the counterion includes, but is not limited to, sodium, potassium, cesium or amine bases, and wherein said amine bases include, but are not limited to, DBU, MTBD, DIPEA, or triethylamine, yields the alkylated support bound moiety available for further reaction with isonicotinoyl chloride to yield an alkylated isonicotinamide derivative. In preferred embodiments, the diversifiable functionality, R_o, includes but is not limited to, branched or unbranched, substituted or unsubstituted alkyl, aryl, and arylalkyl moieties.

Each of the templates synthesized according to the method of the present invention, whether in the solution phase or attached to a solid support, can then be subsequently used in the synthesis of desired scaffold structures.

Shikimic acid based scaffold structures

The above-described epoxyol templates provide useful starting materials for the synthesis of diversifiable scaffold structures. In one particularly preferred embodiment, the synthesis of a

tetracyclic scaffold is achieved by reaction of the epoxyol bound template with a nitrone under transesterification conditions to yield a tetracycle as shown in Figure 13. Tamura and co-workers have described the synthesis of a tricyclic compound by tandem transesterification-cycloaddition reaction of a nitrone methyl ester and a cyclohexen-3-ol. A modified sequence for this tricyclic structure was used to yield the core tetracyclic template (see, Tamura et al. *Tetrahedron* **1995**, *51*, 107; Tamura et al. *Tetrahedron* **1995**, *51*, 119). One of ordinary skill in the art will realize that any commonly used transesterifiction reagent may be employed to yield the desired tetracycle structure, such as the Otera catalyst, $(SCNBu_2Sn)_2O$. Moreover, the nitrone employed in the reaction can also be varied to yield different derivatives of the tetracyclic scaffold. As shown in Figure 13, a benzyl nitrone is synthesized from a benzaldehyde precursor. In other embodiments, other aldehydes, such as any aromatic or aliphatic aldehyde, can be substituted to yield different nitrones. Alternatively, Figure 14 depicts the synthesis of different iodophenyl nitrones from the nitrophenyliodides. These nitrophenyliodides are reduced, preferably with Zn/NH_4Cl, to the N-iodophenylhydroxylamine, followed by condensation with glyoxylic acid monohydrate to form the N-iodophenylnitrones. Any of the abovementioned nitrones, or derivatives thereof can be subsequently reacted with the epoxyol template to yield a desired tetracycle, such as the tetracycle (as shown in Figure 13) and shown in **(II)** below.

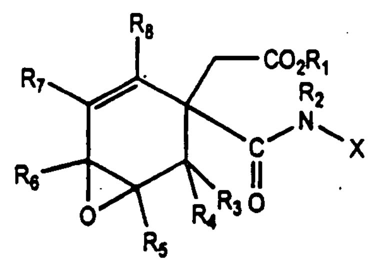


(II)

Referring to **(II)**, R_1-R_9 each independently includes, but is not limited to hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and any substituted or unsubstituted heterocycle wherein said substituted

heterocycle is preferably substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and X includes, but is not limited, to any of the above, a solid support, a biomolecule or polymer. Furthermore, each of the above functionalities may be unsubstituted or substituted with appropriate chemical moieties. In a particularly preferred embodiment, R_2-R_9 are each hydrogen, R_1 is an substituted or unsubstitued alkyl, aryl, or alkylaryl, and X is a solid support unit or hydrogen.

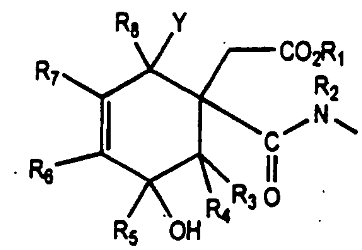
In another particularly preferred embodiment, alternative scaffold structures can be obtained in which the epoxyol bound template is treated with an orthoacetate, such as trimethylorthoacetate to undergo a Johnson ortho-ester-like Claisen rearrangement to yield the ester (1), as shown in Figure 15 and in (III) below.



(III)

Referring to (III), R_1-R_8 each independently includes, but is not limited to, hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X includes, but is not limited to, any of the above, a solid support, a biomolecule or polymer. Furthermore, each of the above functionalities may be unsubstituted or substituted with appropriate chemical moieties. In a particularly preferred embodiment, R_2-R_8 are each hydrogen and R_1 is a lower alkyl group, such as methyl, and X is a hydrogen or a solid support unit.

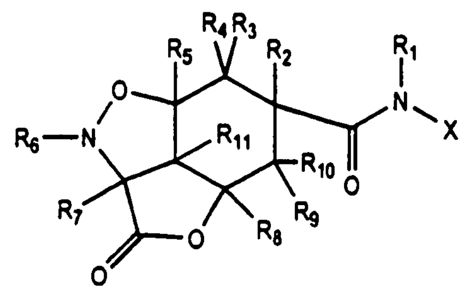
Reaction of this scaffold structure with other reagents also yields alternative diversifiable scaffold structures, as shown in Figure 15. For example, reaction with a palladium allylation catalyst such as $Pd(dba)_2$ and a nucleophile (Y), yields an alternative epoxide opened structure (2), as shown in Figure 15 and (IV) below.



(IV)

Referring to (IV), R_1-R_8 each independently includes, but is not limited to hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X includes, but is not limited to, any of the above, a solid support, a biomolecule or polymer; and Y includes, but is not limited to nucleophiles selected from the group consisting of amine, phenol, maleonate, thiol, carboxylic acid, and azide. Furthermore, each of the above functionalities may be unsubstituted or substituted with appropriate chemical moieties. In a particulary preferred embodiment, R_2-R_8 are each hydrogen and R_1 is a lower alkyl group, such as methyl, X is a hydrogen or a solid support unit, and Y is an amine, phenol, maleonate, thiol, carboxylic acid, or azide.

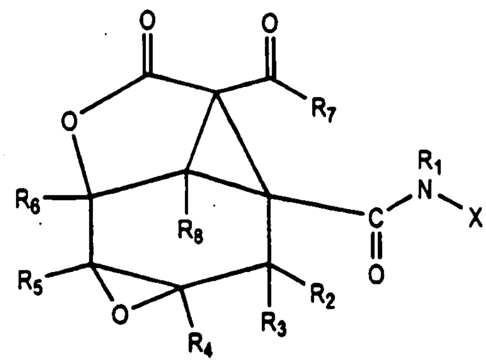
Subsequent reaction with a nitrone, under standard conditions, yields an alternative diversifiable scaffold structure (3), as shown in Figure 15 and (V) below, where the addition of reagents, such as but not limited to, amines or boronic acid, yields diversified structures, as shown in Figure 15.



(V)

Referring to (V), R_1-R_{11} each independently includes, but is not limited to, hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X includes, but is not limited to, any of the above, a solid support unit, a biomolecule or polymer. Furthermore, each of the above functionalities may be unsubstituted or substituted with appropriate chemical moieties. In a particularly preferred embodiment, R_1-R_5 and R_7-R_{11} are each hydrogen, R_6 is a substituted or unsubstituted aryl, alkyl, arylalkyl; and X is hydrogen or a solid support unit.

Additionally, in another particularly preferred embodiment, a different scaffold can be constructed whereby the inventive epoxyol template is treated with an acylating agent including, but not limited to a diketene, to yield the diketone, as shown in Figure 16. Subsequent reaction with tosyl azide yields the diazo β-keto ester (2), as shown in Figure 16. Finally, cyclopropanation with a rhodium or copper catalyst yields the cyclic scaffold structure (3), as shown in Figure 16 and (VI) below, which contains several radially diversifiable moieties.



(VI)

Referring to **(VI)**, R_1-R_8 each independently includes, but is not limited to, hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X includes, but is not limited to any of the above, a solid support unit, a biomolecule or polymer. Furthermore, each of the above functionalities may be unsubstituted or substituted with appropriate chemical moieties. In particularly preferred embodiments, R_1- R_6 and R_8 are each hydrogen, R_7 is a lower alkyl, such as methyl, and X is a hydrogen or a solid support unit.

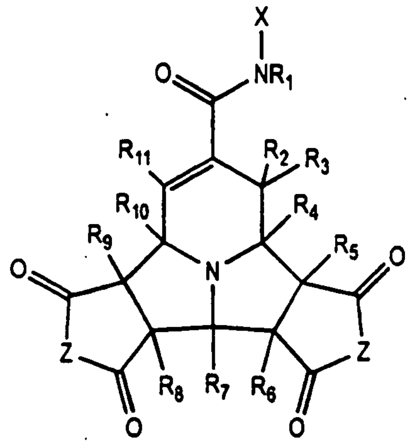
One of ordinary skill in the art will appreciate that the particular functional groups available at any site in the template structures must be compatible with the particular reaction chemistry being utilized in the synthesis of the scaffold structures. Additionally, the compounds described herein contain one or more centers of asymmetry and may thus give rise to enantiomers, diastereomers and other stereoisomeric forms. The present invention is meant to include all such possible stereoisomers as well as their racemic and optically pure forms. Optically active (R) and (S) isomers may be prepared using chiral synthesis, chiral reagents, or resolved using conventional techniques. When the compounds disclosed herein contain olefinic double bonds, it is intended to include both E and Z geometric isomers. Furthermore, the examples and scaffolds, and the functional groups contained therein, presented above are not

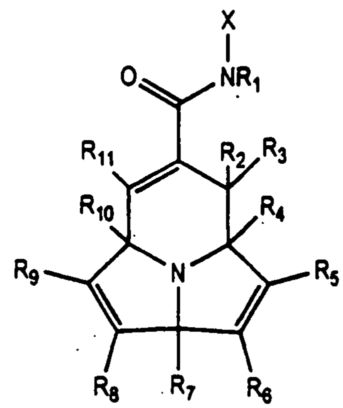
intended to be exclusive; rather all equivalents thereof are intended to be within the scope of the present invention.

Synthesis of Pyridine Based Scaffold Structures

The present invention also provides a method for the synthesis of compounds and complex combinatorial libraries based on isonicotinamide templates in the solution phase or on the solid support, as discussed previously. In preferred embodiments, the synthesis of polycyclic alkaloids is achieved from 1,2-dihydropyridines. As shown in Figures 17 and 18, each of the resulting pentacycles share isonicotinamide as a starting material and feature a 1,2-dihydropyridine synthetic intermediate. Cycloadditions are used in each synthesis to build up structural complexity and functional group manipulations are used to elaborate the rigid core structures.

In particularly preferred embodiments, the solid support bound isonicotinamide can be first converted into an azomethine ylide in the synthesis of diversifiable scaffold structures. For example, in one particularly preferred embodiment, the cup-like pentacyclic piperidine scaffold (1), as shown in Figure 17, can be obtained by reaction of the template with bromoacetopheone, triethylamine and N-methylmaleimide to yield the azomethine ylide. Subsequently, reaction with N-methylmalimide under reflux conditions yields the desired pentacycle, as shown in **(VIIA)** below, wherein Z is N-R, and wherein R is preferably a substituted or unsubstituted alky or aryl mioety and which contains several sites of latent functionality for diversification. One of ordinary skill in the art will realize that the synthesis of the scaffold is not limited to the pentacyclic structure and may also be diversified by employing any double substituted or unsubstituted bond containing an electron withdrawing group, to yield alternative piperidine structures for **(VIIA)**, in which Z is CH_2, O or S, or structures as shown in **(VIIB)**.



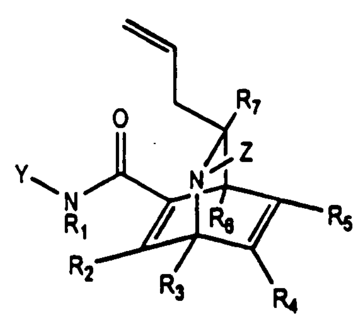


(VIIA) (VIIB)

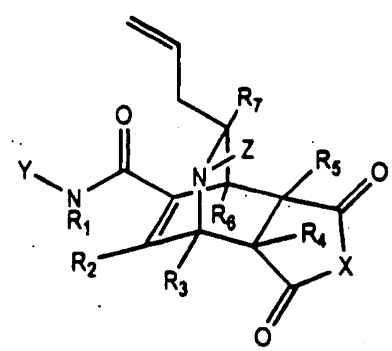
Referring to (VIIA and VIIB), R_1-R_{11} each independently includes hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X is a any of the above, a solid support, a biomolecule or polymer; and Z is NR, wherein R includes but is not limited to any substituted or unsubstituted alkyl or aryl mioety, CH_2, O, or S. In particularly preferred embodiments, R_1 is hydrogen or any aliphatic group, R_2-R_6 and R_8-R_{11} are each hydrogen, R_7 is a benzoyl moiety, X is a hydrogen, or a solid support unit; and in the case of Figure 7a, Z is NR, wherein R includes but is not limited to any substituted or unsubstituted alkyl or aryl mioety.

In another particularly preferred embodiment, the resin bound isonicotinamide template is converted to the allyl derivative, from which isoquinuclidine scaffolds are synthesized, as shown in Figure 18. First, the resin bound template is treated with allyltributyltin to yield the allyl intermediate. One of ordinary skill in the art will realize that this reaction may also be effected stereoselectively to yield stereochemically pure scaffold structures. For example, in one particularly preferred embodiment, the synthesis of an enantiomerically pure compound may be effected by the asymmetric synthesis of 1,2 dihydropyridine as shown in Figure 19, which can

then be used in the synthesis of enantiomerically pure scaffold structures and combinatorial libraries. Figure 20 also depicts a method for the stereoselective synthesis of 1,2-dihydropyridines utilizing a sugar based chiral auxiliary. Alkylation of the pyridine with glucosyl bromide yields the pyridinium salt which is then capable of directing the addition of nucleophiles stereoselectively. In addition to providing stereochemically pure compounds, the inventive method also provides a novel rearrangement of the allyl intermediate as shown in Figure 21. Upon exposure to light, the allyl intermediate undergoes a rearrangement to yield a new intermediate which can subsequently be utilized in the synthesis of the scaffold, thus providing further diversity. The intermediate, as shown in Figures 17 or 18, or any of the intermediates discussed above, may be subsequently reacted with dienophiles, including, but not limited to maleic anhydride, aza-dicarboximide, and dimethylacetylenedicarboxylate, in a Diels-Alder reaction to yield various tricyclic intermediates, as shown in Figure 22 and more generally in (VIIIA and VIIIB), shown below. Subsequent reaction of the imide intermediate with a primary amine, and removal of the protecting group yields alternative isoquinuclidine scaffolds, as shown in Figure 18, and more generally in (VIIIB)



(VIIIA)

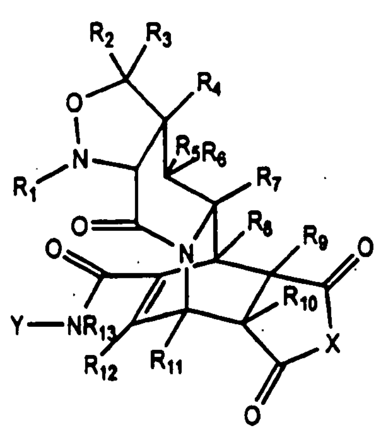


(VIIIB)

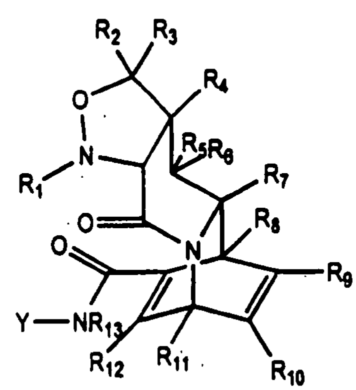
Referring to (VIIIA and VIIIB), R_1-R_7 each independently includes, but is not limited to hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any

functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X includes, but is not limited to NR, wherein R includes but is not limited to any substituted or unsubstituted alkyl or aryl mioety, CH_2, O or S; Y includes, but is not limited to hydrogen, a solid support unit, a polymer or biomolecule; and Z includes, but is not limited to, hydrogen or indole. Furthermore, each of the above functionalities may be unsubstituted or substituted with appropriate chemical moieties. In particulary preferred embodiments, R_1-R_7 are each hydrogen, X is NR, wherein R includes but is not limited to any substituted or unsubstituted alkyl or aryl moiety, Y is a solid support unit, and Z is an indole to generate an ibogamine-like compound, as shown in Figure 18. Furthermore, as shown in Figure 23, an indole substituted allyl scaffold (1) is also capable of undergoing palladium insertion to yield the cyclic structure (2). Reaction with dimethyl sulfate and DBU yields an alternative structure (3) depicted in Figure 23.

In yet another particularly preferred embodiment, the tandem acylation and [(3 + 2] cyclization employed in the shikimic acid based combinatorial library discussed above can also be utilized to generate a polycyclic alkaloid from the deprotected isoquinuclidine scaffold as shown in Figure 18 and (**IXA** and **IXB**) below.



IXA



IXB

Referring to **IXA** and **IXB** above, R_1-R_{13} each independently includes, but is not limited to hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl,thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X includes, but is not limited to, NR, wherein R includes but is not limited to any substituted or unsubstituted alkyl or aryl moiety, CH_2, O or S; andY includes, but is not limited to, hydrogen, a solid support unit, a polymer or biomolecule. Furthermore, each of the above functionalities may be unsubstituted or substituted with appropriate chemical moieties. In particularly preferred embodiments, R_1 is a benzyl, and R_2-R_{13} are each hydrogen, X is NR, wherein R includes but is not limited to any substituted or unsubstituted alkyl or aryl moiety, and Y is a solid support unit.

One of ordinary skill in the art will appreciate that the particular functional groups available at any site in the isonicotinamide-based template structures must be compatible with the particular reaction chemistry being utilized in the synthesis of the scaffold structures. Additionally, the compounds described herein contain one or more centers of asymmetry and may thus give rise to enantiomers, diastereomers and other stereoisomeric forms. The present invention is meant to include all such possible stereoisomers as well as their racemic and optically pure forms. Optically active (R) and (S) isomers may be prepared using chiral synthesis, chiral reagents or resolved using conventional techniques. When the compounds disclosed herein contain olefinic double bonds, it is intended to include both E and Z geometric isomers. Furthermore, the templates and scaffolds, and the functional groups contained therein and the reagents utilized, presented above are not intended to be exclusive; rather all equivalents thereof are intended to be within the scope of the presently claimed invention.

Reactions at latent functionality in the inventive scaffolds

Once the inventive scaffolds have been synthesized as discussed above, diversification reactions may be employed at each of the different latent functionality sites present in the scaffold. One of ordinary skill in the art will appreciate that the reactivity of a particular functionality must be considered when selecting a reagent for diversification.

In one particularly preferred embodiment, diversification reactions are employed on the shikimic acid based tetracyclic scaffold. Examples of specific reactions to which some or all of the shikimic acid based tetracyclic systems can be subjected in solution or on the solid support include i) addition of nucleophiles (primary and secondary amines) to the γ-lactone function as shown in Figures 24, 25 and 26; ii) functionalization of the free hydroxyl with electrophiles (for example, isocyanates, anhydrides, or acid chlorides as depicted in Figure 27); iii) opening of the epoxide with nucleophiles, such as amines, under ytterbium catalysis (see, for example, Ryan et al. *Tetrahedron* **1973**, *29*, 3649; Lindsay Smith et al. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1200) as shown in Figures 28 and 29, or thiols or hydroxyls as shown in Figures 30 and 31) ; iv) cleavage of the N-O bond of tetrahydroisoxazole to release a 1,3 amino alcohol that can be functionalized with various electrophiles such as acid chlorides, sulfonyl chlorides, or isocyanates; and v) functionalization at the iodide in the aromatic ring. For example, functionalization of the iodide in the aromatic ring can be effected by conversion to such structures as amines, amides, aromatic rings, alkenes, alkynes, and heterocycles using palladium-catalyzed chemistry, as shown in Figure 32 which depicts various diversification reactions that can be employed on an iodoaromatic ring, such as Buchwald-Hartwig aminations, Heck (see, Heck, R.F. *In Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Permagon Press: Oxford, 1991; Vol. 4, pp. 833-863; Hiroshige et al. *Tetrahedron Lett.* **1995**, *36*, 4567) and Stille couplings (see, Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; Despande, M.S. *Tetrahedron Lett.* **1994**, *35*, 5613) Sonogashira/Castro-Stephens couplings (see, Sonogashira, et al. *Tetrahedron Lett.* **1975**, 4467; Stephens, R.D.; Castro, C.E. *J. Org. Chem.* **1963**, *28*, 3313; Young et al. *J. Am. Chem. Soc.* **1994**, *116*, 10841; Collini et al. *Tetrahedron Lett.* **1997**, *38*, 7963; Odingo, J.; Sharpe, B.A.; Oare, D. Presented at the 213th National Meeting of the American Chemical Society, San Francisco, CA, April 1997; ORGN 574), Suzuki and Stille couplings, and carbonylations. More specifically, Figure 33 depicts palladium cross-coupling reactions at the aryl iodide using the Sonogashira-Castro-Stephens, Suzuki and Stille reactions. Furthermore, resulting aryl alkynes can undergo rhodium-catalyzed hydroacylation and azide cycloaddition as shown in Figure 34, and nitrone and nitrile oxide cycloaddition as shown in Figure 35.

In another particularly preferred embodiment, the isoquinuclidine core as shown in Figure 36, can be diversified by reaction at potential diversity dites such as the amine, the bridge carbon and the amide functionality. For example, the amide may be functionalized using a Mitsunobu reaction to generate alcohols such as straight chain, branched, and cyclic alcohols. In

particularly preferred embodiments, the alcohol should not have an unprotected site that could be acylated, such as an amine, or thiol. The bridge amine can be subjected to reaction to yield chloroformates, by reacting alcohols with phosgene, and anything that can acylate or alkylate an amine, such as alkyl bromides, mesylates, and aldehydes to name a few. The bridge carbon may also be functionalized to yield an allyl and any allyl derivative of allyltributyltin, thiazole or indole, but is not limited to these functionalities. Furthermore, the carboximide may be functionalized by reaction with reagents including, but limited to, amines, amino acids, and alcohols. Figure 37 also depicts the use of amino acids to generate more diversity. Additionally, Figure 38 depicts the potential diversity sites for the cup-like pentacyclic scaffold structure.

One of ordinary skill in the art will realize that the above examples are representative of the reactions that can be used to diversify the templates, scaffolds, compounds, and libraries of compounds of the presently claimed invention and are not intended to be exclusive. Rather, all equivalents thereof are intended to be within the scope of the presently claimed invention. A skilled artisan will be able to readily identify those reagents capable of reacting to create further diversity at selected sites in the inventive scaffold structures to generate compounds and libraries of compounds reminiscent of natural products.

Combinatorial Methods for the Synthesis of Complex Natural Product-Like Libraries

According to the method of the present invention, the synthesis of libraries from the above-described scaffold structures can be performed using established combinatorial methods for solution phase, solid phase, or a combination of solution phase and solid phase synthesis techniques. The synthesis of combinatorial libraries is well known in the art and has been reviewed (see, e.g., "Combinatorial Chemistry", Chemical and Engineering News, Feb. 24, 1997, p. 43; Thompson, L.A., Ellman, J.A., *Chem. Rev.* **1996**, *96*, 555.) One of ordinary skill in the art will realize that the choice of method will depend upon the specific number of compounds to be synthesized, the specific reaction chemistry, and the availability of specific instrumentation, such as robotic instrumentation for the preparation and analysis of the inventive libraries. In particularly preferred embodiments, the reactions to be performed on the inventive scaffolds to generate the libraries are selected for their ability to proceed in high yield, and in a stereoselective fashion, if applicable.

In one embodiment of the present invention, the inventive libraries are generated using a solution phase technique. Traditional advantages of solution phase techniques for the synthesis of combinatorial libraries include the availability of a much wider range of organic reactions, and

the relative ease with which products can be characterized. Notable disadvantages of solution phase techniques includes the inability to easily synthesize libraries of compounds containing very large numbers, such as one million or more library members, because one reaction vessel must be provided for each library member, and the inability to use excess reagents without time-consuming purification steps, such as chromatography. Recently, however, advances have been made in solution phase synthesis techniques such as the use of a "covalent scavenger" which selectively removes from solution via covalent bond formation. The "covalent scavenger" is essentially a solid phase bound nucleophile or electrophile that reacts with these excess reagents. (Kaldor, Eli Lilly, Frechet et al., *Tetrahedron Lett.*, 21, 617 (1980)). In a preferred embodiment, for the generation of a solution phase combinatorial library, a parallel synthesis technique is utilized, in which all of the products are assembled separately in their own reaction vessels. In a particularly preferred parallel synthesis procedure, a microtitre plate containing n rows and m columns of tiny wells which are capable of holding a few milliliters of the solvent in which the reaction will occur, is utilized. It is possible to then use n variants of reactant A, such as a carboxylic acid, and m variants of reactant B, such as an amide to obtain n x m variants, in n x m wells. One of ordinary skill in the art will realize that this particular procedure is most useful when smaller libraries are desired, and the specific wells can provide a ready means to identify the library members in a particular well.

In another more particularly preferred embodiment of the present invention, a solid phase synthesis technique is utilized, in which the desired scaffold structures are attached to the solid phase directly or though a linking unit, as discussed above. Advantages of solid phase techniques include the ability to more easily conduct multi-step reactions and the ability to drive reactions to completion because excess reagents can be utilized and the unreacted reagent washed away. Perhaps one of the most significant advantages of solid phase synthesis is the ability to use a technique called "split and pool", in addition to the parallel synthesis technique, develped by Furka. (Furka et al., *Abstr. 14th Int. Congr. Biochem.*, Prague, Czechoslovakia, 1988, *5*, 47; Furka et al., *Int. J. Pept. Protein Res.* 1991, *37*, 487; Sebestyen et al., *Bioorg. Med. Chem. Lett.*, 1993, *3*, 413.) In this technique, a mixture of related compounds can be made in the same reaction vessel, thus substantially reducing the number of containers required for the synthesis of very large libraries, such as those containing as many as or more than one million library members. As an example, the solid support scaffolds can be divided into n vessels, where n represents the number species of reagent A to be reacted with the scaffold structures. After reaction, the contents from n vessels are combined and then split into m vessels, where m

represents the number of species of reagent B to be reacted with the scaffold structures. This procedure is repeated until the desired number of reagents is reacted with the scaffold structures to yield the inventive library.

The use of solid phase techniques in the present invention may also include the use of a specific encoding technique. Specific encoding techniques have been reviewed by Czarnik. (Czarnik, A.W., *Current Opinion in Chemical Biology*, **1997**, *1*, 60.) As used in the present invention, an encoding technique involves the use of a particular "identifiying agent" attached to the solid support, which enables the determination of the structure of a specific library member without reference to its spatial coordinates. One of ordinary skill in the art will also realize that if smaller solid phase libraries are generated in specific reaction wells, such as 96 well plates, or on plastic pins, the reaction history of these library members may also be identified by their spatial coordinates in the particular plate, and thus are spatially encoded. It is most preferred, however for large combinatorial libraries, to use an alternative encoding technique to record the specific reaction history.

Examples of particulary preferred alternative encoding techniques that can be utilized in the present invention include, but are not limited to, spatial encoding techniques, graphical encoding techniques, including the "tea bag" method, chemical encoding methods, and spectrophotometric encoding methods. Spatial encoding refers to recording a reaction's history based on its location. Graphical encoding techniques involve the coding of each synthesis platform to permit the generation of a relational database. Examples of preferred spectrophotometic encoding methods include the use of mass spectroscopy, fluorescence emission, and nuclear magnetic resonance spectroscopy. In a most preferred embodiment, chemical encoding methods are utilized, which uses the structure of the reaction product to code for its identity. Decoding using this method can be performed on the solid phase or off of the solid phase. One of ordinary skill in the art will realize that the particular encoding method to be used in the present invention must be selected based upon the number of library members desired, and the reaction chemistry employed.

In an exemplary embodiment of the method of the present invention, more than 2,000,000 members of a shikimic acid based library can be generated. The preferred method of the invention begins with the attachment of one or more spacers to the linking reagent, preferably a photolinker. Subsequently, the resin can be pooled, divided into two portions, and one enantiomer of epoxycyclohexenol carboxylic acid coupled to each pool. After pooling and division into three portions, iodobenzyl nitrone acids can be coupled resulting in a total of 18

tetracyclic scaffolds. The stereoselective synthesis of the library of complex compounds reminiscent of natural products can be completed by reaction with 30 terminal alkynes, 62 primary amines, and finally 62 carboxylic acids, employing a split and pool technique at each step. Each of the reagents utilized are preferably selected for their ability to generate diversity and for their ability to react in high yield. As one of ordinary skill in the art will realize, the use also of a skip codon (Combs et al. *J. Am. Chem. Soc.* 1996, *118*, 287), or "blank", at each step yields further diversity. Furthermore, in particulary preferred embodiments, after each reaction step, the beads are "tagged" to encode the particular reaction choice employed. Preferred alkynes for use in the presently claimed invention include, but are not limited to acetaldehyde ethyl propargyl acetal, tert-butyl 1-methyl-2-propynyl ether, 4-(tert-butyl) phenylacetylene, tert-butyldimethylsilyl acetylene, 2-(3-butynloxy)tetrahydro-2H-pyran, 1-chloro-4-ethynylbenzene, 1,4-decadiyne (50% in hexane), 1,5-decadiyne, 3-dibutylamino-1-propyne, m-diethynylbenzene, 3,3-dimethyl-1-butyne, 1-dimethylamino-2-propyne, 1-dodecyne, ethyl ethynyl ether (50% in hexanes), ethynyl p-tolyl sulfone, 1-ethynyl-4-fluorobenzene, 1-ethynylcyclohexene, ethynylestradiol 3-methyl ether, 2-ethynylpyridine, 4-ethynyltoluene, 1,5-hexadiyne (50% in hexane), 1-hexyne, 5-hexynenitrile, methyl propargyl ether, 2-methyl-1-buten-3-yne, methyl-N-propargylbenzylamine, 1,8-nonadiyne, 1-pentyne, 4-phenyl-1-butyne, 3-phenyl-1-propyne, phenylacetylene, propargyl ether, propargyn-1H-benzotriazole, N-(propargyloxy)phthalimide, N-propargylphthalimide, propargyltriphenylphosphonium bromide, proiolaldehyde diethyl acetal, tetrahydro-2-(2-propynyloxy)-2H-pyran, triethylsilylacetylene, tripropargylamine, 2-(3-burynloxy)tetrahydro-2H-pyran, 3,5-dimethyl-1-hexyn-3-ol, 1,1-diphenyl-2-propyn-1-ol, 1-ethynyl-1-cyclohexanol, 1-ethynyl-4-fluorobenzene, 9-ethynyl-9-fluorenol, 1-ethynylcyclopentanol, 1-heptyne, 3-methyl-1-pentyn-3-ol, 2-phenyl-3-butyn-2-ol, and propiolaldehyde diethyl acetal. Preferred primary amines include, but are not limited to, allylamine, 2-amino-1-propene-1,1,3-tricarbonitrile, 3-amino-1H-isoindole hydrochloride, 3-amino-5-methylisoxazole, aminoacetaldehyde diethyl acetal, aminoacetaldehyde dimethyl acetal, aminoacetonitrile bisulfate, 4-(2-aminoethyl)benzenesulfonamide, 4-(2-aminoethyl)morpholine, 2-(2-aminomethyl)pyridine, 1-(2-aminoethyl)pyrrolidine, 2-aminoindan hydroxchloride, (R)-(-)-1-aminoindan, (S)-(+)-1-aminoindan, 2-(aminomethyl)-15-crown-5, 4-(aminomethyl)benzenesulfonamide hydrochloride, (aminomethyl)cyclopropane, 2-pyrenemethylamine hydrochloride, 3-(aminomethyl)pyridine, 4-(aminomethyl)pyridine, 3-aminopropionitrile fumarate, 1-(3-aminopropyl)-2-pyrrolidinone, 1-(3-aminopropyl)imidazole, 3-aminopropyltrimethoxysilane, (R)-(+)-3-aminoqauinuclidine dihydrochloride, (S)-(-)-3-

aminoquinuclidine dihydrochloride, ammonia (0.5 M in dioxane), benzylamine, S-benzylcysteamine hydrochloride, (R)-(+)-bornylamine, butylamine, cyclobutylamine, cyclohexanemethylamine, cyclohexylamine, cyclopentylamine, cyclopropylamine, (R)-(+)-cycloserine, 3-(diethoxymethylsilyl)propylamine, 3,4-dimethoxyphenethylamine, 4-(dimethylamino)benzylamine dihydrochloride, 3-dimethylaminopropylamine, N,N-dimethylethylenediamine, ethylamine (2.0 M in THF), 1-ethylpropylamine, 2-fluoroethylamine hydrochloride, 4-fluorophenethylamine, furfurylamine, geranylamine, 3-fluorobenzylamine, (1R, 2R, 3R, 5S)-(-)-isopinocampheylamine, (1S, 2S, 3S, 5R)-(+)-isopinocampheylamine, isopropylamine, 2-methoxybenzylamine, 4-methoxybenzylamine, 2-methoxyethylamine, 2-methoxyphenethylamine, 3-methoxyphenethylamine, 4-methoxyphenethylamine, 3-methoxypropylamine, methylamine (2.0M in THF), (-)-cis-myrtanylamine, 1-napthylenemethylamine, 3-nitrobenzylamine hydrochloride, 4-nitrophenethylamine hydrochloride, octylamine, phenethylamine, trans-2phenylcyclopropylamine hydrochloride, 2-phenylglycinonitrile hydrochloride, piperonylamine, propargyl amine, (R)-(-)-tetrahydrofurfurylamine, (S)-(+)-tetrahydrofurfurylamine, N,N,2,2-tetramethyl-1,3-propanediamine, 2-thiopheneethylamine, 2,2,2-trifluoroethylamine, tryptamine, veratrylamine, 2-(2-aminoethyl)pyridine, 3-(aminomethyl)pyridine, (R)-(-)-sec-butylamine, (S)-(+)-sec-butylamine, (R)-(-)-1-cyclohexylethylamine, (S)-(+)-1-cyclohexylethylamine, isoamylamine, (R)-(+)-a-methylbenzylamine, (S)-(-)-1-(1-napthyl)ethylamine, 4-(trifluoromethyoxy)benzylamine, and 3-(trifluoromethyl)benzylamine. Preferred carboxylic acids include, but are not limited to, acetic acid, 4-acetoxybenzoic acid, acetylsalicyclic acid, acrylic acid, m-anisic acid, o-anisic acid, p-anisic acid, benzoic acid, 2-butynoic acid, (3-carboxypropyl)trimethylammonium chloride, 3-chloropropionic acid, crotonic acid, cyanoacetic acid, 3-cyanobenzoic acid, 4-cyanobenzoic acid, cyclohexanecarboxylic acid, cyclopentanecarboxylic acid, cyclopentylacetic acid, cyclopropanecarboxylic acid, 3,4-dihydro-2,2-dimethyl-4-oxy-2H-pyran-6-carboxylic acid, 1,4-dihydro-2-methylbenzoic acid, 3-dimethylaminobenzoic acid, 4-dimethylaminobenzoic acid, N,N-dimethylglycine, ferroceneacetic acid, formic acid, trans-3-furanacrylic acid, 2-furoic acid, 3-furoic acid, furylacrylic acid, 2,4-hexadienoic acid (Sorbic acid), isobutyric acid, isonicotinic acid, isovaleric acid, levulinic acid, linolenic acid, (+)-menthoxyacetic acid, (-)-menthoxyacetic acid, methacrylic acid, methoxyacetic acid, (R)-(-)-a-methoxyphenylacetic acid, (S)-(+)-a-methoxyphenylacetic acid, 2-methoxyphenylacetic acid, 3-methoxyphenylacetic acid, 4-methoxyphenylacetic acid, 1-methyl (1S, 2R)-(+)-cis-1,2,3,6-tetrahydrophthalate, mono-methyl

glutarate, mono-methyl phthalate, mono-methyl terephthalate, [1R-(1-a, 2b, 3a)]-(+)-3-methyl-2-(nitromethyl)-5-oxocyclopentaneacetic acid, 4-(3-methyl-5-oxo-2-pyrazolin-1-yl)benzoic acid, 6-methylchromone-2-carboxylic acid, 3,4-(methylenedioxy)phenylacetic acid, 1-methylindole-2-carboxylic acid, nicotinic acid, 5-nitro-2-furoic acid, 4-nitrobenzoic acid, 4-nitrophenylacetic acid, 3-nitropropionic acid, 2-norbornaneacetic acid, orotic acid monohydrate, (S)-(+)-2-oxo-4-phenyl-3-oxazolidineacetic acid, anti-3-oxotricyclo[2.2.1.0(2,6)]heptane-7-carboxylic acid, phenylacetic acid, phenylpropiolic acid, phthalylsulfathiazole, picolinic acid, propionic acid, 2-pyrazinecarboxylic acid, 2-pyridylacetic acid hydrochloride, 3-pyridylacetic acid hydrochloride, 4-pyridylacetic acid hydrochloride, (2-pyrimidylthio)acetic acid, pyruvic acid, tetrahydro-2-furoic acid, tetrahydro-3-furoic acid, thioctic acid, 2-thiopheneacetic acid, 3-thiopheneacetic acid, 2-thiophenecarboxylic acid, 3-thiophenecarboxylic acid, 2-thiopheneglyoxylic acid, (α,α,α-trifluoro-p-tolyl)acetic acid, vinylacetic acid, acetoxyacetic acid, 2-benzofurancarboxylic acid, cinnoline-4-carboxylic acid, 3,5-diido-4-pyridone-1-acetic acid, 3,3-dimethylacrylic acid, ferrocenecarboxylic acid, 5-methoxy-1-indanone-3-acetic acid, 1-methyl-2-pyrrolecarboxylic acid, 3-oxo-1-indancarboxylic acid, trans-3-(3-pyridyl)acrylic acid, 3-(2-thienyl)acrylic acid, α,α,α-trifluoro-m-toluic acid, α,α,α-trifluoro-o-toluic acid, and α,α,α-trifluoro-p-toluic acid. Additionally, Figure 39 depicts a plan for the synthesis of over 46.5 million complex molecules.

In another exemplary embodiment, the present invention provides a method for synthesizing over 30,000,000 members of an isoquinuclidine library as depicted in Figure 40. First, 63 derivatized isonicotinamide templates are provided and reacted with allyltributyltin and TeocCl to yield a racemic mixture, thus providing 126 compounds. Subsequent reaction with maleic anhydride, 63 amino acids, and 63 amines, yields 500,094 compounds. Further reaction with 3 nitrone isomers, and 20 arylboronic acids yields over 30,000,000 complex compounds reminiscent of natural products.

Subsequent characterization of the library members can be performed using standard analytical techniques, such as mass spectrometry, Nuclear Magnetic Resonance Spectroscopy, and gas chromatrograpy. One of ordinary skill in the art will realize that the selection of a particular analytical technique will depend upon whether the inventive library members are in the solution phase or on the solid phase. As but one example, Figures 41 though 44 more particularly depict the synthesis and analysis of a test library of shikimic acid-based compounds; these examples are not intended to limit the scope of the present invention, however. In yet another example, Figure 45 depicts the synthesis of a test library of isoquinuclidine-based compounds, as also described in more detail in the Examples.

Uses

The methods, compounds and libraries of the present invention can be utilized in various disciplines. For example, one aspect of the present invention concerns a method for identifying natural product-like small molecules from the inventive libraries of compounds, which modulate the biological activity of a biological target, such as a protein, nucleic acid, lipid or combination thereof. In one preferred embodiment, the compounds of the present invention are utilized in chemical genetics assays to alter, i.e. inhibit or initiate, the action of such biological molecules. Alternatively or additionally, the compounds may be used in in vitro assays, or any other system that allows detection of a chemical or biological function.

In a particularly preferred embodiment of the invention, one or more inventive compounds is contacted with a biological target having a detectable biochemical activity. Such biological targets include, for example, enzymes, receptors, subunits involved in the formation of multimeric complexes. Such multimeric complex subunits may be characterized by catalytic capabilities (such as, for example, an ability to catalyze substrate conversion), or may alternatively be primarily active in binding to one or more other molecule. The biological target can be provided in the form of a purified or semi-purified composition, a cell lysate, a whole cell or tissue, or even a whole organism. The level of biochemical activity is detected in the presence of the compound, and a statistically significant change in the biochemical activity, relative to the level of biochemical activity in the absence of the compound, identifies the compound as a modulator, e.g. inhibitor or potentiator of the biological activity of the target protein. In some cases, particularly where assays are done on whole cells or organisms, the effect of the chemical compound may be to alter the amount, in addition to or instead of the activity, of the particular biological target. "Modulators", therefore, are chemical compounds that alter the level or activity of a particular target molecule.

In one particularly preferred embodiment of the present invention, multiple compounds are assayed simultaneously in a high-throughput format, preferably allowing simultaneous analysis of at least 500,000 compounds, preferably at least 1,000,000 compounds, and most preferably at least or more than 2,000,000 compounds. One such format, referred to herein as "nanodroplet format" is described in US patent application 08/951,930, entitled "Droplet Assay System", which is incorporated herein by reference. In brief, the format involves ordered or stochastic arrays of small volume (preferably about 50-200 nL, most preferably about 100 nL) droplets into which chemical compounds to be assayed are distributed. Those of ordinary skill in the art will readily appreciate that this nanodroplet format can be employed for any of a large

variety of assays. Any assay whose result may be observed in the context of a discrete liquid droplet is appropriate for use with the present invention. Preferred read-out assays for use in accordance with the present invention analyze chemical or biological activities of test compounds. Read-out assays can be designed to test in vitro or in vivo activities. Example 1 describes the preferred droplet assay procedure, and Examples 2- 4 describe particularly preferred assays for analysis of the inventive chemical compounds.

As discussed above, once a specific desired effect on a biological target has been associated with a particular compound of the inventive library, the compounds of the present invention may be utilized as a therapeutic agent for a particular medical condition. A therapeutic agent for use in the present invention may include any pharmacologically active substances that produce a local or systemic effect in animals, preferably mammals, or humans. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal or human. The therapeutic agent may be administered orally, topically or via injection by itself, or additionally may be provided as a pharmaceutical composition comprising the therapeutic agent and a biologically acceptable carrier. The inventive compositions can be, but are not limited to an aqueous solutions, emulsions, creams, ointments, suspensions, gels, and liposomal suspensions. Particularly preferred biologically acceptable carriers include but are not limited to water, saline, Ringer's solution, dextrose solution and solutions of ethanol, glucose, sucrose, dextran, mannose, mannitol, sorbitol, polyethylene glycol (PEG), phosphate, acetate, gelatin, collagen, Carbopol, and vegetable oils. It is also possible to include suitable preservatives, stabilizers, antioxidants, antimicrobials, and buffering agents, for example including but not limited to BHA, BHT, citric acid, ascorbic acid, and tetracycline. The therapeutic agents of the presently claimed invention may also be incorporated or encapsulated in a suitable polymer matrix or membrane, thus providing a sustained-release delivery device suitable for implantation near the site to be treated locally.

As one of ordinary skill in the art will realize, the amount of the therapeutic agent required to treat any particular disorder will of course vary depending upon the nature and severity of the disorder, the age and condition of the subject, and other factors readily determined by one or ordinary skill in the art.

In alternative embodiments, the compounds and libraries of the present invention may also be used for the development of cosmetics, food additives, pesticides, and lubricants to name a few. Furthermore, the compounds and libraries of the present invention may also be used for

the development of novel catalysts and materials. For example, the inventive compounds may be useful as ligands for transition metal catalysts and the inventive libraries may be useful for the rapid identification of novel ligands. These compounds and libraries of compounds may also function by acting in concert with a particular transition metal catalyst to effect a particular desired chemical reaction. Additionally, the inventive compounds and libraries of compounds are also useful in the area of materials science. Because of the reactive moieties present in these compounds, molecules such as lipids and other polymeric materials may be attached and thus generate potentially important biomaterials.

One of ordinary skill in the art will realize that the present invention is not intended to be limited to the abovementioned uses, but rather may be employed in many contexts and disciplines.

Furthermore, the specific examples presented below, and also the specific examples presented in the Appendix (for the more detailed experimentals for the synthesis of compounds and libraries of compounds, the characterization of said compounds and libraries of compounds, and the testing of the biological activity of said compounds and libraries of compounds) are intended to more particulary describe the present invention, but are not intended to limit the scope of the presently claimed invention.

Examples

Example 1: Nanodroplet assay:

The ability of the preferred procedure utilized for the library synthesis to controllably release compounds from the individual 90 μ diameter beads into nanodroplet containing engineered wells enables the use of these miniaturized cell-based assays to detect specific characteristics of library members. In a particularly preferred embodiment of the invention, the compounds in an inventive encoded combinatorial library are attached to beads through a photocleavable linker. Each bead is labeled with a tag that identifies the bound compound. Additionally, the concentration of the test compound released in the droplet can be controlled by controlling the time of exposure to UV radiation. The amount of compound released in any particular experiment, of course, will depend on the efficiency of bead loading and the extent of bead functionalization. Figure 46 depicts the photorelease of an inventive compound.

In particular, the present invention specifically contemplates the screening of the inventive compounds, especially libraries of these compounds in assays designed to detect their

protein-binding properties (e.g., small molecule inactivation of protein targets or small molecule activation of protein targets).

Example 2: Assay to detect activation of gene expression: The inventive compounds and libraries of compounds synthesized by the inventive method are tested for activation of a luciferase reporter gene with pathway specific promoters such as a TGF-β responsive promoter/enhancer. The luciferase gene is a particularly preferred reporter gene because the determination of the expressed luciferase enzyme is rapid, easy to perform and detection is extremely sensitive. Furthermore, luciferase is a monomeric protein that does not require any post-translational processing and can thus be measured as a genetic reporter immediately upon translation. As shown in Figure 47, 8 different pools, each containing 64 different isolated compounds selected from the shikimic acid test library as described in Appendix A, were tested for the ability to induce luciferase activity and all were found to activate the reporter gene to various extents. Interestingly, KC233, an isolated compound selected from the inventive isoquinuclidine library, does not activate the reporter gene and furthermore also prohibits TGF-β from activating the reporter gene. Figure 48 depicts this in greater detail.

These results suggest that compounds **43{5,8,1}** and **43{6,8,1}**, as described in the library synthesis below, are useful for the activation of a signaling pathway that results in activation of the 3TP promoter, and that KC233, a member of the isoquinuclidine library is effective in preventing TGF-β-induced activation of the 3TP promoter/enhancer. One of ordinary skill in the art will realize that other reporter genes can be utilized to test the ability of the inventive compounds and libraries of compounds to promote different cellular responses. Exemplary reporter genes include, but are not limited to secreted alkaline phosphatase (seap), β-lactamase, chloramphenicol transferase (cat), and green fluorescent protein.

Example 3: Cell Proliferation Studies

In another illustrative embodiment, the inventive compounds and libraries of compounds were tested for their ability to inhibit cell proliferation in mink lung cells. Figure 49 depicts the ability of each of the specific pools of 64 compounds (1 μM per compound) selected from the shikimic acid test library to inhibit cell proliferation. These results suggest that the inventive compounds and libraries of compounds are useful as inhibitors of cell proliferation, and thus may also be useful as potential therapeutics for cancer or other conditions such as autoimmune diseases in which the inhibition of cell proliferation, specifically tumor cell proliferation or hematopoietic cell growth is important. Furthermore, Figure 50 depicts the ability f KC233, a member of the inventive isoquinuclidine library (KC233 shown in Figure 48), to arrest mink

lung cells in the S-phase of the cell cycle. After treatment of mink lung cells with 10 μM KC233 for 40 hours, the DNA content corresponding to the G1, G2 and M phases decreases, and the corresponding DNA content associated with the S phase increases. Thus, these results suggest that KC233 is useful as a therapeutic for arresting lung cell cancers. Additionally, the ability of KC233 to act as a general cell cycle arresting agent suggests its ability to function analogously to other cell-cycle arresting drugs. For example, hydroxyurea, the currently cytotoxic agent of choice for treatment of chronic myelocytic leukemia, also arrests cells in the S-phase. Another example of a cell-cycle arresting drug in which the cell cycle is arrested in mitosis (M-phase) is the well-known anticancer drug paclitaxel (Taxol), currently approved for ovarian cancer and head and neck cancer. One of ordinary skill in the art will realize that these represent only a few examples of cell-cycle arresting drugs, and that the inventive compounds and libraries of compounds may function as analogues of other cell-cycle arresting drugs.

General Materials and Methods for Assays:

Cell Culture: Mv1Lu mink lung epithelial cells were obtained form the American Type Culture Collection (catalog # CCL64). Clone 6f is a stably transfected derivative of Mv1Lu cells containing the p3TPLux reporter plasmid as well as the construct $MF_p,3T_1[D]$ (see Stockwell, B.R.; Schreiber, S.L. *Curr. Biol.* **1998**, *8*, 761). Mv1Lu and 6f cells were cultured in DMEM with 10% FBS, 100 units/mL penicillin G sodium, 100 μg/mL streptomycin sulfate and 100 μM each of the amino acids Ala, Asp, Glu, Gly, Asn, and Pro.

Luciferase Assay: 2.0×10^5 6f cells were seeded in each 35 mm well of a six well dish in 10% FBS. After 20 hours, the cells were washed once and incubated in DMEM containing 0.2 % FBS and the non-essential amino acids (NEAA) and the reagent of interest (e.g., library pool, KC233, or TGF-β) for 25 to 30 hours. Cells were incubated on ice for 15 minutes, washed three times with HBSS and lysed in extraction buffer (25 mM glycylglycine, pH 7.8, 15 mM $MgSO_4$, 4 mM egta, 1%Triton X, 1 mM DTT, 1 mM PMSF) by shaking gently at 4°C for 30 minutes. The lysates were centrifuged for 5 minutes at 10,000 g at 4°C and stored on ice. 100 μL of lysate was added to 150 μL of assay mixture (25 mM glycylglycine pH 7.8, 15 mM $MgSO_4$, 4 mM egta, 15 mM K_2HPO_4 pH 7.8, 1 mM DTT, 4 mM ATP) and 150 μL of luciferin buffer (25 mM glycylglycine pH 7.8, 15 mM $MgSO_4$, 4 mM egta, 10 mM DTT, 167 μM D-luciferin). This mixture was placed in a 500 μL microfuge tube inside a glass scintillation vial, and luminescence was detected by counting in single photon mode (SPM) on a Beckman LS 6500 liquid scintillation counter for 15 seconds. The error bars reported represent plus or minus one standard deviation. All experiments were performed multiple times in triplicate.

Growth Inhibition Assay: Mv1Lu cells were seeded in 6 well clusters (20,000 cells per well) and allowed to attach overnight in 10% serum. Media was changed to 1% FBS with or without the test compound. After four days the cells were washed, trypsinized and counted. The cell number reported represent live cells, since dead cells detach and are washed away by this protocol.

Example 4: Testing the inventive libraries for the ability to act as a ligand for the receptor of human growth hormone:

Another interesting application for the complex radially arrayed combinatorial libraries of the presently claimed invention is as a ligand for the receptor for human growth hormone, which induces homodimerization of the receptor and initiates the intracellular growth hormone signalling pathway, as depicted in Figure 3. The "hot spot", which is a small patch of residues identified as being responsible for the majority of the binding energy between hGH and its receptor is an excellent target for the library.

Example 5: Test Library Synthesis for ibogamine-like compounds (as shown in Figure 45): With the viability of the synthetic route proven, rigorous quality control experiments required for the synthesis of large collections of polycyclic alkaloid natural product-like molecules have been undertaken. Polystyrene resin (400-450 um) loaded with a photo-cleavable linker was chosen for the building block screening studies. The resin was chosen from a screen of solid supports with a photo-cleavable linker because it provided the best balance between loading and reaction kinetics.

As shown in Figure 45 the building block studies began with the coupling of eleven Fmoc-amino acids onto polystyrene resin (400-450 μm) loaded with a photocleavable linker. After removal of the Fmoc protecting group and acylation with isonicotinoyl chloride, a portion of each sample was photolyzed and analyzed by TLC and LCMS. Ten of the eleven building blocks were converted in >90% purity to the desired product (see Chart A below).

In the second step, each of the resulting isonicotinamides was treated with allyltributyltin and TeocCl to yield N-acyl-1,2-dihydropyridines. A portion of each sample was photolyzed and analyzed by TLC and LCMS. All samples were converted in >90% purity to the desired product (See Chart B below).

In the third step, each of the ten N-acyl-1,2-dihydropyridines was then reacted with maleic anhydride. Each sample was photolyzed and analyzed by TLC and LCMS to ensure that all of the building blocks from the first step would perform equally well in two batch steps (a-

allylation of N-acylpyridinium salt and Diels-Alder reaction). All samples were converted in >90% purity to the desired product (see Chart C below).

Assured that all of the building blocks selected in the first step could withstand the two batch steps, a single isoquinuclidine was scaled up for the next step. In the fourth step, an isoquinuclidine with glycine in the first building block position was scaled up for testing in the imide forming reaction. Of 20 amines tested in the 2-pyridone mediated imide forming reaction 18 were converted in > 90% purity to the desired product (See Chart D below).

In the final building block testing step, a single isoquinuclidinium salt was scaled up for building block testing in the nitrogen alkylation/acylation reaction (see Chart E below).

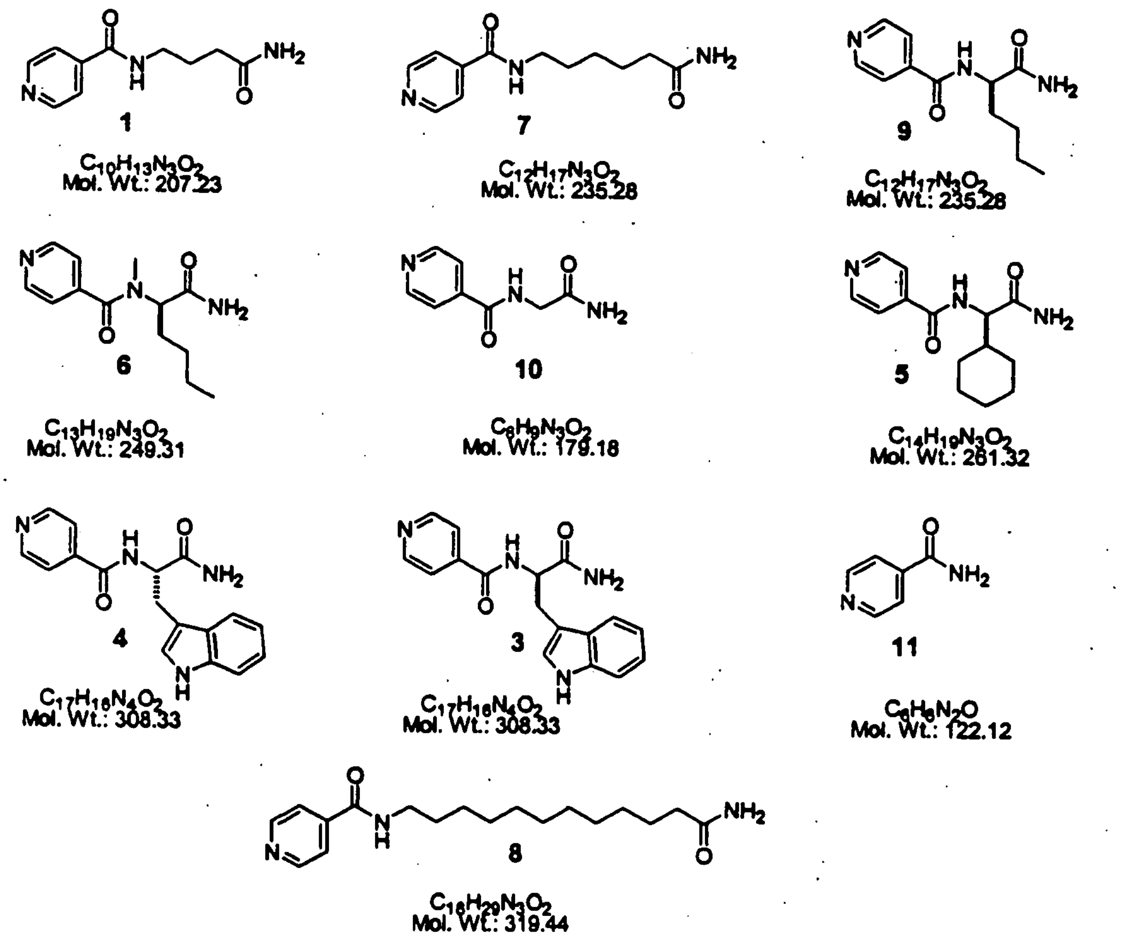
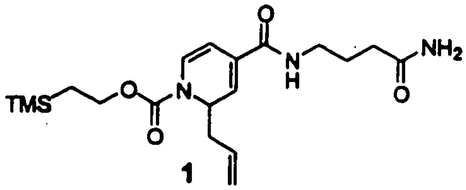


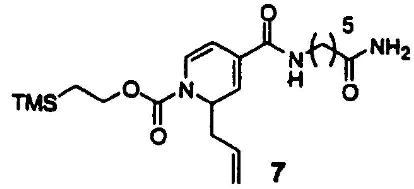
CHART A

0



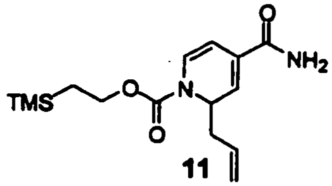
1

$C_{19}H_{31}N_3O_4Si$
Mol. Wt.: 393.55



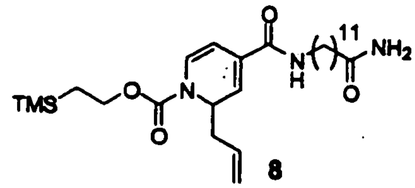
7

$C_{21}H_{35}N_3O_4Si$
Mol. Wt.: 421.61



11

$C_{15}H_{24}N_2O_3Si$
Mol. Wt.: 308.45



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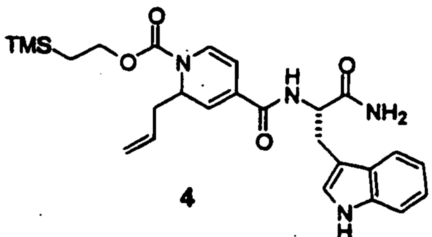
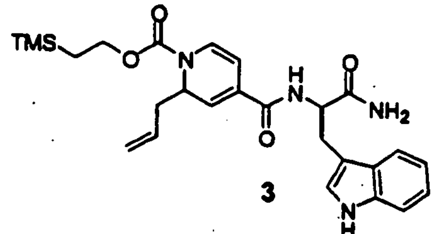
$C_{27}H_{47}N_3O_4Si$
Mol. Wt.: 505.77



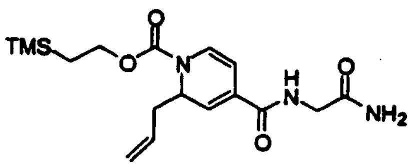
4

$C_{26}H_{34}N_4O_4Si$
Mol. Wt.: 494.66



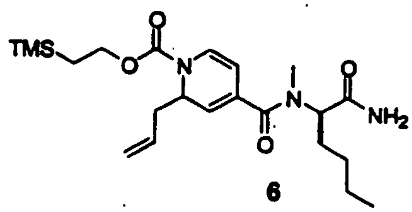
3

$C_{26}H_{34}N_4O_4Si$
Mol. Wt.: 494.66



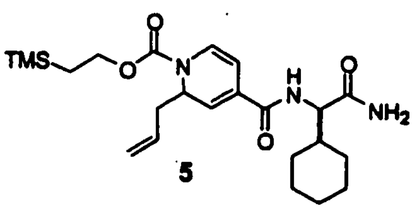
10

$C_{17}H_{27}N_3O_4Si$
Mol. Wt.: 365.50



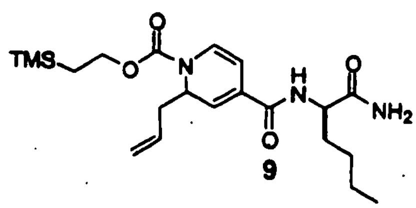
6

$C_{22}H_{37}N_3O_4Si$
Mol. Wt.: 435.63



5

$C_{23}H_{37}N_3O_4Si$
Mol. Wt.: 447.64

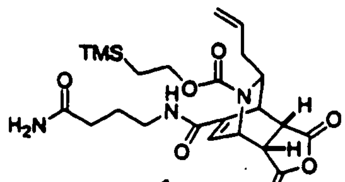


9

$C_{21}H_{35}N_3O_4Si$
Mol. Wt.: 421.61

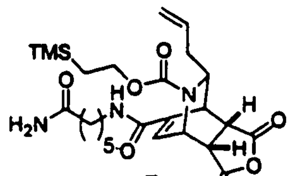
CHART B

0



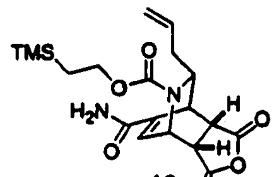
1

$C_{23}H_{33}N_3O_7Si$
Mol. Wt.: 491.61



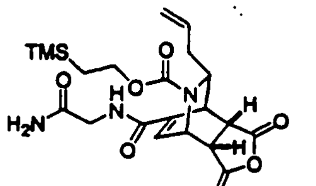
7

$C_{25}H_{37}N_3O_7Si$
Mol. Wt.: 519.66



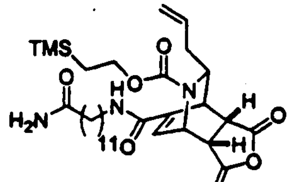
10

$C_{19}H_{26}N_2O_6Si$
Mol. Wt.: 406.51



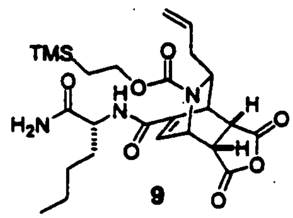
5

$C_{21}H_{29}N_3O_7Si$
Mol. Wt.: 463.56



8

$C_{31}H_{49}N_3O_7Si$
Mol. Wt.: 603.82



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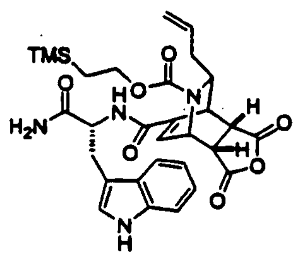
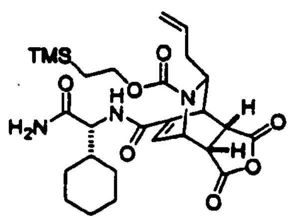
$C_{25}H_{37}N_3O_7Si$
Mol. Wt.: 519.66



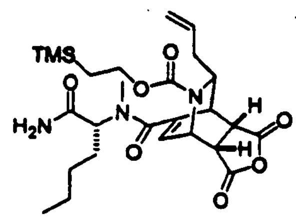
4

$C_{30}H_{36}N_4O_7Si$
Mol. Wt.: 592.72



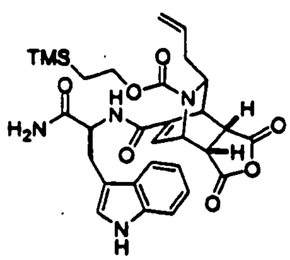
5

$C_{27}H_{39}N_3O_7Si$
Mol. Wt.: 545.70



6

$C_{26}H_{39}N_3O_7Si$
Mol. Wt.: 533.69



3

$C_{30}H_{36}N_4O_7Si$
Mol. Wt.: 592.72

Chart C

0

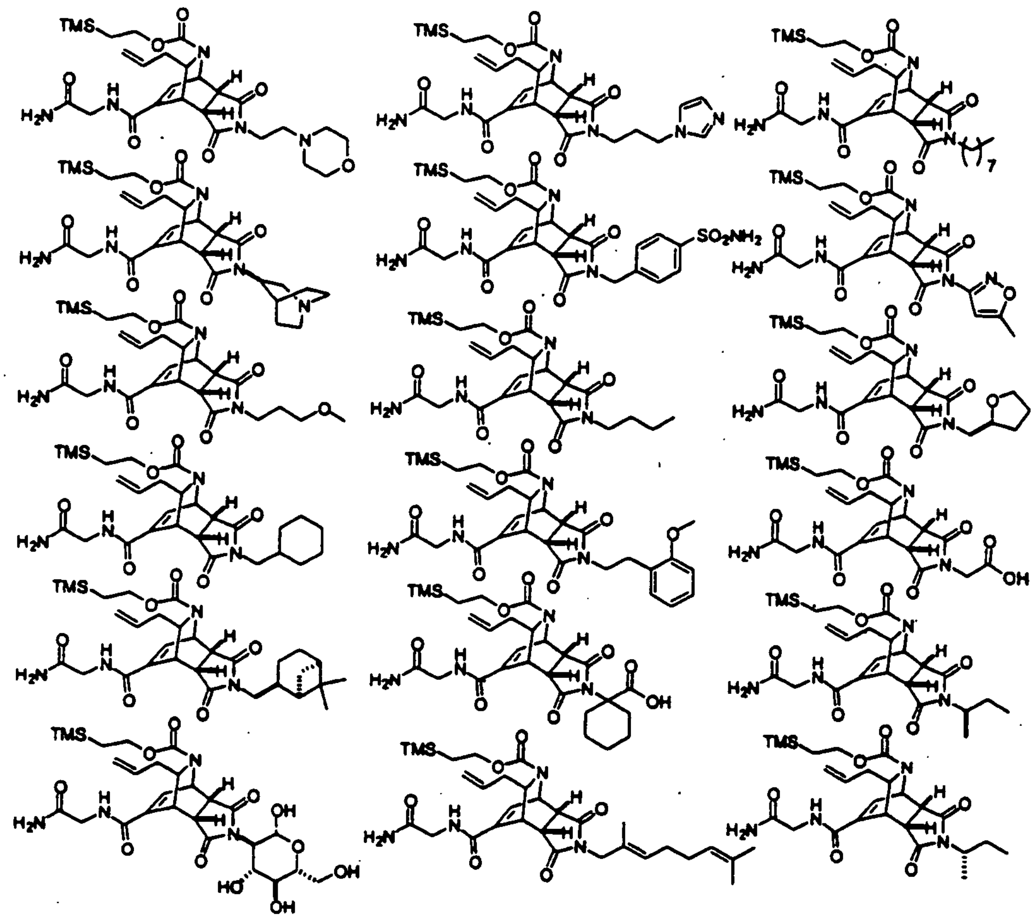


CHART D

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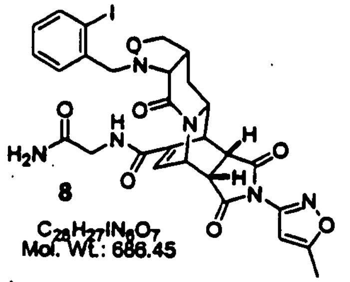
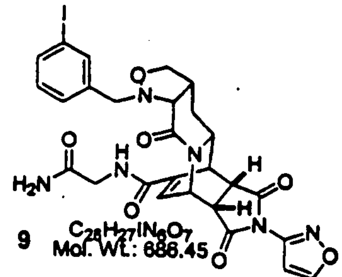
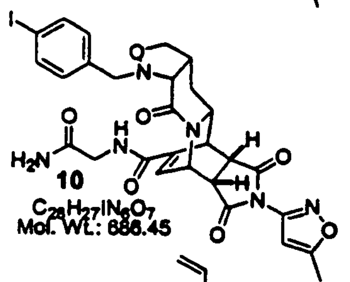


8

$C_{28}H_{27}IN_6O_7$
Mol. Wt.: 686.45

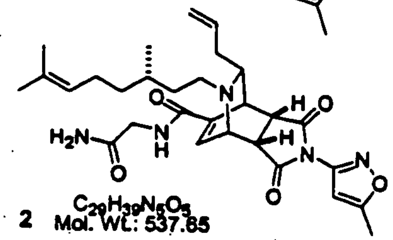


9 $C_{28}H_{27}IN_6O_7$
Mol. Wt.: 686.45

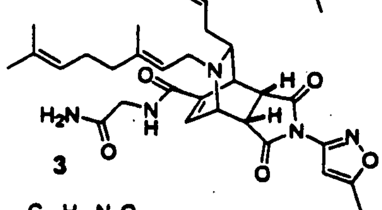


10

$C_{28}H_{27}IN_6O_7$
Mol. Wt.: 686.45

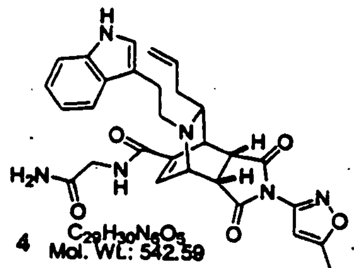


2 $C_{29}H_{39}N_5O_6$
Mol. Wt.: 537.65

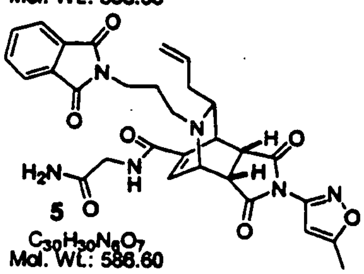


3

$C_{29}H_{37}N_5O_6$
Mol. Wt.: 535.63

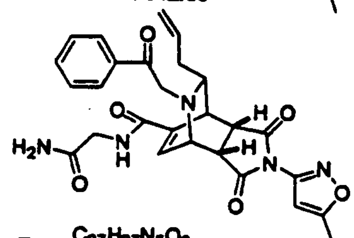


4 $C_{29}H_{30}N_6O_6$
Mol. Wt.: 542.59

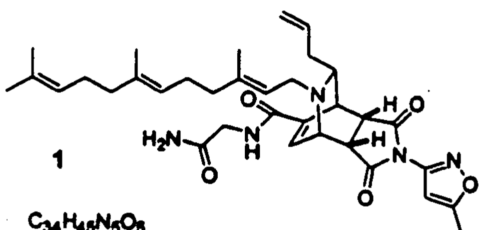


5

$C_{30}H_{30}N_6O_7$
Mol. Wt.: 586.60

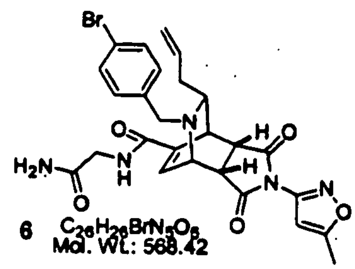


7 $C_{27}H_{27}N_5O_6$
Mol. Wt.: 517.53



1

$C_{34}H_{45}N_5O_6$
Mol. Wt.: 603.75



6 $C_{26}H_{26}BrN_5O_6$
Mol. Wt.: 568.42

CHART E

APPENDIX

A: Methods and Experimentals f r the Synthesis and Evaluation of a Library of Shikimic Acid Based Library of Polycyclic Small Molecules

I. General Experimental Details:

General. Solution phase reactions were performed in oven- or flame-dried glassware under positive N_2 pressure. Small-scale solid phase reactions (5-10 mg resin) were performed in 500 µL polypropylene Eppendorf tubes (VWR Scientific Products; 20170-310) with mixing provided by a Vortex Genie-2 vortexer (VWR 58815-178, setting V2-V3) fitted with a 60 microtube insert. Medium-scale solid phase reactions (20-500 mg resin) were performed in 2 mL fritted polypropylene Bio-Spin® chromatography columns (Bio-Rad Laboratories, Hercules, CA; 732-6008) or 10 mL fritted polypropylene PD-10 columns (Pharmacia Biotech, Piscataway, NJ; 17-0435-01) with 360° rotation on a Barnstead-Thermolyne Labquake™ Shaker (VWR 56264-306). Large-scale solid phase reactions (>500 mg resin) were performed in silanized 50 or 100 mL fritted glass tubes equipped for vacuum filtration and N_2 bubbling. The tubes were silanized by treatment with 20% dichlorodimethylsilane/CH_2Cl_2 for 15 min, MeOH for 15 min, followed by oven heating at 120 °C for at least 2 h.

After small-scale reactions, resin samples were transferred to 2 mL BioSpin® columns via vacuum cannula. Resin samples in polypropylene columns were washed on a Vac-Man® Laboratory Vacuum Manifold (Promega, Madison, WI; A7231) fitted with nylon 3-way stopcocks (Biorad 732-8107). Resin samples in glass tubes were washed in the reaction vessels with alternating periods of N_2 bubbling and vacuum draining. The following <u>standard wash procedure</u> was used: 3 × THF, 3 × DMF (Method A) or NMP (Method B), 3 × iPrOH, 3 × DMF/NMP, 3 × CH_2Cl_2, 3 × DMF/NMP, 3 × CH_3CN, 3 × THF, 3 × CH_2Cl_2.

Resin samples were then transferred via spatula to 500 µL Eppendorf tubes and suspended in Ar-degassed HPLC grade CH_3CN. The tubes were wrapped with parafilm and fixed with rubber bands to a 2" x 3" piece of cardboard that had been wrapped with aluminum foil. The tubes were then placed on a vortexer (setting S1-S2) under a UVP High Intensity Longwave UV Lamp (Fisher Scientific, Pittsburgh, PA; 11-984-79) at a distance of 3 inches (~21.7 mW/cm^2). Photocleavage products were recovered by filtration and evaporation or by sampling of the supernatant.

Atom numbers shown in structures below refer only to NMR peak assignments and not to CAS or trivial nomenclature. Compound numbers followed by **R** represent molecules still attached to the solid support.

Sources. Reagents were obtained from Advanced Chemtech (Louisville, KY), Aldrich Chemical (Milwaukee, WI), Eastman Chemicals (Rochester, NY), Fluka (Milwaukee, WI), GFS Chemicals (Powell, OH), Novabiochem (San Diego, CA), Pierce (Rockford, IL), or Strem Chemicals (Newburyport, MA) and used without further purification. Tentagel S NH_2 was obtained from Rapp Polymere (Germany). Solvents were obtained from Mallinckrodt or E. Merck. Wash solvents were used as received. Reaction solvents were distilled under N_2 as follows: Tetrahydrofuran (THF), diethyl ether (Et_2O), and dimethoxyethane (DME) from sodium/benzophenone ketyl; methylene chloride (CH_2Cl_2), ethyl acetate (EtOAc), benzene, toluene, pyridine, 2,6-lutidine, and *N,N*-diisopropylethylamine (DIPEA) from calcium hydride; methanol (MeOH) from magnesium methoxide. Anhydrous *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), 1-methyl-2-pyrrolidinone (NMP), and trimethyl orthoformate (TMOF) were obtained from Aldrich in SureSeal™ bottles. Water (H_2O) was double distilled.

Purification and Analysis. Flash chromatography was performed on E. Merck 60 230-400 mesh silica gel. TLC was performed on 0.25 mm E. Merck silica gel 60 F_{254} plates and visualized by UV (254 nm) and cerium ammonium molybdate (CAM). HPLC was performed on a Nest Group (Southborough, MA) Hypersil C18 100 Å 3 μ 4.6 mm x 6 cm column using a flow rate of 3 mL/min and a 4 min gradient of 0-99.9% CH_3CN in H_2O /0.1% TFA, constant 0.1% MeOH with diode array UV detection. Melting point determinations were performed on a Laboratory Devices (Cambridge, MA) Mel-temp apparatus and are uncorrected (benzoic acid, lit. 122-123 °C, found 119.0-121.5 °C). Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. IR spectra were recorded on a Nicolet 5PC FT-IR Spectrometer with peaks reported in cm^{-1}. NMR spectra were recorded on Varian Inova 600 and Bruker DMX500, AM500, and AM400 instruments. Chemical shifts are expressed in ppm relative to TMS (0.00 ppm) or residual solvent signals ($CDCl_3$ 7.26 ppm/77.0 ppm; CD_3CN 1.93 ppm/1.3 ppm, CD_3OD 3.30 ppm/49.0 ppm). Peak assignments were made based on extensive homonuclear decoupling and/or two-dimensional DQF-COSY, TOCSY, and NOESY experiments. Mass spectra were obtained on JEOL AX-505H or SX-102A mass spectrometers by electron impact ionization (EI), chemical ionization (CI) with ammonia (NH_3), or fast atom bombardment ionization (FAB) with glycerol or 3-nitrobenzyl alcohol/sodium iodide (NBA/NaI) matrices. Time-of-flight electrospray ionization (TOF-ESI) data were obtained on a Micromass LCT mass spectrometer. Tandem high pressure liquid chromatography-mass spectrometry (LC-MS) data were obtained on a Micromass Platform II mass spectrometer in atmospheric pressure chemical ionization (AP-CI) mode attached to a Hewlett-Packard Series 1050 HPLC system. LC-MS chromatography was performed on a Hewlett-Packard ODS Hypersil 5 μ, 2.1 mm x 10 cm column using a flow

rate of 0.4 mL/min and a 5 min gradient of 30-90% CH_3CN in H_2O, constant 0.1% formic acid with detection at 214 nm.

Atom numbers shown in structures below refer only to NMR peak assignments and not to CAS or trivial nomenclature. Compound numbers followed by **R** represent molecules still attached to the solid support.

II. General Description of Experimental Plan:

Library Validation Protocols. Split-pool synthesis provides the theoretical means to synthesize the full matrix of every combination of building blocks in a multi-step synthesis. Such large numbers of molecules will likely be required for successful outcomes in chemical genetic screens. However, these syntheses present enormous analytical challenges. We have developed a four-stage validation protocol in order to provide maximum confidence that a complex, split-pool synthesis of encoded molecules yields the anticipated products in high purity and efficiency. The first three protocols are concerned with the synthetic molecules and the fourth with the encoding step.

First, the suitability of the reaction sequence for library synthesis was demonstrated by execution of the entire reaction sequence six times, each time using different building blocks. The fully elaborated final products, **42a-f**, as shown in Figure 51, were recovered in 80-90% purity following photolysis. These products, as well as the 20 intermediates preceding them (**38a**, **38d**, **39a-f**, **40a-f**, **41a-f**), were fully characterized by multidimensional ^{1}H-NMR, HR-FAB-MS, TLC, and HPLC. This experiment showed that the reaction sequence could be used to synthesize library members in satisfactory purity.

Second, potential building blocks were tested by reaction with a selected substrate at each step (**Figure 52**). While it is impossible to test the complete matrix of building block combinations, this experiment indicated which building blocks are compatible with the coupling reactions. Thus, 50 alkynes (**Figure 53**) were tested in reactions with iodobenzyltetracycle **39d**, 87 amines (**Figure 54**) in reactions with alkynylbenzyltetracycle **40d**, and 98 acids (**Figure 55**) in reactions with γ-hydroxyamide **41d**. Nearly every commercially available terminal alkyne was tested, along with a variety of amines and acids representing different steric and electronic functional groups. Photocleavage products were analyzed by HPLC and LC-MS(certain acid-sensitive products were also analyzed by TLC and FAB-MS) and their purities and percent conversions were estimated from these data (**Figure 56**). There were no obvious trends among the alkynes that were unsuitable for the Sonogashira/Castro-Stephens reaction, however, in the aminolysis and esterification reactions, electron poor amines and electron rich or enolizable acids generally did not react with suitable efficiency. In addition, several of the acids were insoluble under the reaction conditions. Of the building blocks tested, 23 alkynes, 54 amines, and 44 acids

reacted with greater than or equal to 90% conversion and purity. These building blocks, along with a limited number of less optimal candidates (generally reacting with greater than or equal to 70% conversion and purity), were selected for inclusion in library synthesis.

Third, a small test library was generated from iodobenzyltetracycle **39b** (**Figure 57**) in order to investigate whether any unforeseen complications, such as interactions between building blocks coupled at different sites, might arise during synthesis in a split-pool format. The building blocks were carefully selected such that every product within each final acylated pool would have a unique mass (**Figure 58**), allowing analysis by LC-MS. Thus, the tetracycle-containing resin was divided into eight portions and the seven alkynes were coupled to the first seven portions. The eighth portion was left as the parent aryl iodide, representing a "skip codon". (Combs et al., *J. Am. Chem. Soc.* **1996**, *118*, 287). After pooling and splitting, the seven amines were coupled and the eighth portion of resin was left as the lactone-closed skip codon. Finally, after a third round of pooling and splitting, the seven acids were coupled and the eighth portion was left as the free C-6 hydroxyl skip codon. Because all eight final pools, designated **43{X,X,1}** through **43{X,X,8}**, (Test library compounds are designated as 43 {R_a, R_b, R_c} where R_a signifies the alkyne building block, R_b signifies the amine building block, and R_c signifies the acid building block. Pools of compounds are signified by Rn=X where X represents all eight building blocks at a given position). contained the same eight γ-butyrolactone compounds corresponding to the aminolysis skip codon, a total of 456 compounds was generated.

Each pool was photocleaved to yield a mixture of 64 compounds that were analyzed by LC-MS (**Figure 59**). Of the 456 expected masses, all 456 (100%) were detected at some level, 418 (92%) were detected at greater than or equal to 10% of the average intensity for the given pool, and 400 (88%) were detected at greater than or equal to 20% of the average intensity for the given pool. All of the weak signals resulted from compounds having one of two building blocks at the amine position. 1(-3-Aminopropyl)-2-pyrrolidinone (**Amine 6**) is known to cyclize to DBN with loss of H_2O. Since strong bases had been found to be incompatible with our linker-support combination, this building block was excluded from full-scale library synthesis. The skip codon (**Amine 1**) left lactone-closed tetracycles that were partially hydrolyzed during the final acylation step. As a result, during full-scale library synthesis, the aminolysis skip codon pool was set aside before the final pooling, splitting, and acylation steps.

Binary Encoding. Assuming an ideal, efficient split-pool synthesis, each support carries a single compound. Several solutions to the problem of compound identification have been developed, falling into two general categories: recursive deconvolution and encoding (Czarnik, A. W. *Curr. Opin. Chem. Biol.* **1997**, *1*, 60). Since recursive deconvolution requires several rounds of resynthesis, we chose the particularly powerful *binary* encoding strategy, having used

this method successfully in previous work (Combs et al., *J. Am. Chem. Soc.* **1996**, *118*, 287; Czarnik, A.W. Curr. Opin. Chem. Biol. 1997, 1, 60; Kapoor et al. *J. Am. Chem. Soc.* **1998**, *120*, 23). Still's polyhaloaromatic EC-GC tags, **44**, were selected since they are relatively unreactive and can be coupled directly to the polystyrene backbone of beads using mild carbene insertion chemistry (**Figure 60**) (Ohlmeyer et al. *Proc. Natl Acad. Sci. USA* **1993**, *90*, 10922; Nestler et al. *J. Org. Chem.* **1994**, *59*, 4723). Unfortunately, the published procedures gave inconsistent and unsatisfactory results in our hands. Referring to Figure 60 in the discussion below, substitution of the reported rhodium bis(trifluoroacetate) catalyst with a bulkier rhodium bis(triphenylacetate) catalyst (Callot et al. *Tetrahedron* **1985**, *41*, 4495) suppressed solution-phase diazoketone dimerization and substantially improved the efficiency of tag-bead coupling to form cycloheptatrienes **45**. We also found that, after reaction with an initial set of tags, attachment of subsequent tags to the same beads required multiple couplings. It is possible that the initial reactions occurred at the most accessible sites in the polymer, making subsequent reactions more difficult. Finally, the reaction conditions for oxidative cleavage of the tags from **45** with ceric ammonium nitrate (CAN) were optimized, reducing the required cleavage time to 10 min from the reported 4 h. This improved the yields of the polyhaloaromatic alcohol products, **46**, and allowed rapid and consistent analysis by EC-GC.

Full-Scale Library Planning and Synthesis. Completion of the validation protocols above set the stage for full-scale encoded library synthesis. First, building blocks were selected for each step of the synthesis (**Figure 51**). ω-Aminocaproic acid and glycine were selected as spacer elements with the "no spacer" skip codon providing a third structure for **37**. Use of both enantiomers of epoxycyclohexenol **7** resulted in six structures for **38**. Inclusion of all three iodobenzyl nitrone carboxylic acids **11b-d** led to 18 iodobenzyltetracycle structures for **39**.

The three remaining diversity positions, corresponding to the Sonogashira/Castro-Stephens, lactone aminolysis, and C-6 acylation reactions, allowed the use of substantially larger numbers of building blocks. Optimal use of the binary encoding tags dictates that 2^n–2 building blocks should be used at a given position. This accounts for one skip codon (the "all one" code) and allows for exclusion of the undesirable "all null" code that cannot be differentiated from a failed tagging reaction. As a practical matter, coupling of up to 2^6–2 = 62 building blocks at a given step was deemed feasible.

Only 2^5–2 = 30 building blocks were selected for the Sonogashira/Castro-Stephens reaction because of the relatively small number of available terminal alkynes. Most of the alkynes that reacted efficiently during building block screening (**Figure 53**) were selected. Several racemic alkynes were also included, although diastereomeric products would likely result. Furtherm re, several alkynols were included, despite their potential reactivity in the final

acylation reaction. Control experiments indicated that these hydroxyl groups were efficiently acylated by a variety of alkyl and aromatic acids under the DIPC-mediated coupling conditions. Coupling of 30 different alkynes with exclusion of a 31st skip codon portion would result in 558 structures for **40**.

Wider selections of building blocks were available at the amine and acid positions. For each reaction, 62 building blocks were selected, representing a range of sizes and functional groups (**Figures 54 and 55**). Coupling of 62 different amines with exclusion of a 63rd aminolysis skip codon portion would result in 35,154 structures for **41**. As discussed above, the 558 lactone-closed compounds corresponding to the aminolysis skip codon would not react at the final acylation step. Therefore, the total number of final library compounds, **42**, resulting from acylation with 62 acids and exclusion of a 63rd skip codon portion is calculated as follows: $[(62 \times 558 = 34,596) \times 63 = 2,179,548] + 558 = 2,180,106$ compounds.

Synthesis of three copies of the library was planned, based upon a calculation that indicates that three copies should be screened to ensure 95% confidence that every compound has been sampled (Nolan, G.P., FACS Screening Web Page. http://www.stanford.edu/group/nolan/FACSscrn.html (accessed Jun 1999)). Although this calculation does not address the number of copies required to ensure that every possible compound has been synthesized, we recognized that, if necessary, the library could be resynthesized on larger scale in the future.

Library synthesis began with coupling of Fmoc-protected Geysen linker to 90 μm TentaGel S NH_2. After deprotection, the resin, **36**, was split into three portions by weight and labeled with the tags corresponding to the spacer position. For the fourth validation protocol, after each tagging step in the synthesis, several beads were removed from every portion of the resin and the tags were cleaved and analyzed to ensure adequate incorporation levels. Fmoc-Aca-OH and Fmoc-Gly-OH were then coupled to two of the portions and deprotected under standard conditions. The resin, **37**, was pooled, mixed, and split into two equal portions. After tagging, one enantiomer of epoxycyclohexenol **7** was coupled to each portion. Resin **38** was then pooled, mixed, and split into three equal portions for tagging and reactions with iodobenzyl nitrones **11b-d** to yield resin **39**. These tetracycle-containing resins were pooled, mixed, and split into 31 equal portions. Each was tagged and the appropriate 30 terminal alkynes were coupled using the Sonogashira/Castro-Stephens reaction. The 31st portion of resin was set aside as the skip codon. Resin **40** was pooled, mixed, and split into 63 portions. In this case, the 63rd portion of resin, corresponding to the aminolysis skip codon, was 1/63rd the size of the other 62 portions. This modification was required to avoid overrepresentation of lactone-closed compounds in the completed library. The 62 large portions of resin were tagged and reacted with

the appropriate amines to yield resin **41**. The 63rd skip codon portion was set aside for the remainder of the synthesis to avoid hydrolysis of the lactone-closed compounds during the final acylation step. The remaining 62 portions of resin were pooled, mixed, and split into 63 equal portions. After tagging, the appropriate 62 acids were coupled and the 63rd portion of resin was left as the unreacted C-6 hydroxy compounds. Finally, the 63 acylation portions and the lactone aminolysis skip codon portion were pooled and mixed to yield the final library **42**, calculated to contain three copies of 2,180,106 compounds. The entire process was completed by two of us (D.S.T. and M.A.F.) working over a period of three weeks. The bulk of this time was spent verifying that the encoding tags had successfully coupled to every portion of the resin during each step of the synthesis.

Cell Permeation and Pathway Modulation. It seemed worthwhile to begin an analysis of these compounds by screening the 456-compound test library (**Figure 57**) in cellular assays even before the full-scale library was completed. Although our compounds were designed to contain structural features common to natural products, we had no general sense of their ability to either permeate cells or alter cellular pathways.

These initial studies relied upon traditional non-miniaturized assays, requiring more material than was contained on a single synthesis bead. Thus, the test library was screened as mixtures of compounds cleaved in bulk. The eight final pools, **43{X,X,1}** through **43{X,X,8}**, each contained 64 compounds. The compounds in each pool were photolyzed from the resin, recovered, and dissolved in DMSO at an estimated concentration of 1 mM per compound (64 mM overall) (Based upon previous results a 50% yield was assumed). The eight pools, assayed at concentrations up to 10 μM per compound, showed no suppression of rapamycin-based growth inhibition in *S. cerevisiae* (The rapamycin concentration was 100nM). In addition, none of the pools, assayed at concentrations up to 12.5 μM per compound, showed inhibitory activity in a *Xenopus laevis* oocyte extract assay that indicates modulation of the cyclin B degradation pathway.

However, all eight pools showed a significant inhibitory effect on mink lung cell proliferation when assayed at a concentration of 1 μM per compound (**Figure 61**). Moreover, when the library was assayed at a concentration of 250 nM per compound, pool **43{X,X,8}** (**Figure 62**), was found to activate a TGF-β-responsive reporter gene (Carcamo et al. *J. Mol. Cell. Biol.* **1995**, *15*, 1573) in a stably transfected mink lung cell line (**Figure 63**) (Stockwell et al., *Curr. Biol.* **1998**, *8*, 761) Since this library is not encoded with chemical tags, a recursive deconvolution strategy was used to investigate this activity further.

The 64 compounds in **43{X,X,8}** were resynthesized as eight pools, designated **43{X,1,8}** through **43{X,8,8}**, each containing eight different compounds. Each pool was aminolyzed with

a different amine and all pools were acylated with **Acid 8**. As a negative control, pool **43{X,X,3}** was also resynthesized as eight pools, **43{X,1,3}** through **43{X,8,3}**. Surprisingly, pool **43{X,8,3}**, assayed at a concentration of 1 μM per compound, was a stronger activator of the TGF-β-responsive reporter gene than any of the other 15 eight-compound pools or either of the parent 64-compound pools (data not shown).

A final round of resynthesis deconvoluted pool **43{X,8,3}**, yielding single compounds **43{1,8,3}** through **43{8,8,3}**. These eight compounds and all of the 16 intermediates preceding them were recovered in high purity as determined by ^{1}H-NMR and HR-TOF-ESI-MS analysis. All 24 compounds were screened and compounds **43{5,8,3}** and **43{6,8,3}** were found to activate the TGF-β-responsive reporter gene (**Figure 64**). However, the alkynylbenzyltetracycle (**43{5,1,1}** and **43{6,1,1}**) and γ-hydroxyamide (**43{5,8,1}** and **43{6,8,1}**) precursors to these compounds were even more active. The six active compounds were purified by silica gel chromatography and reassayed, verifying that the desired major product is responsible for the activity in each case. The EC_{50} for the strongest activator, **43{6,1,1}**, is approximately 50 μM.

Discovery of these compounds, while somewhat fortuitous, gave us a measure of confidence in the cell permeating and pathway modulating properties of members of the library. These results also highlight the shortcoming of screening mixtures of compounds. Active compounds may be masked by competing cytotoxic, cytostatic, or antagonistic compounds in the same pool. Alternatively, activity may arise from synergistic effects between two or more compounds, making deconvolution to a single structure impossible. For these reasons, we generally avoid screening mixtures in high-throughput chemical genetic screens.

Chemical Genetic Screens Using Compounds Released from Single Beads. Solid phase synthesis was originally developed to facilitate the purification of peptides from reaction mixtures. Much of the more recent solid phase organic synthesis has been used for a similar purpose, but involves non-oligomeric small molecules. Split-pool synthesis provides a new and arguably more powerful incentive for performing solid phase organic synthesis: It yields large numbers of spatially segregated small molecules. To take full advantage of this feature, assay formats must be developed that use compounds derived from single beads. In our early studies of assay formats using single beads, two such systems were used. Binding-based assays were performed by detecting soluble proteins that had been recruited to individual beads via their interactions with a tethered small molecule (see, Combs et al. *J. Am. Chem. Soc.* **1996**, *118*, 287; Kapoor et al. *J. Am. Chem. Soc.* **1998**, *120*, 23; Morken et al. *J. Am. Chem. Soc.* **1998**, *120*, 30). Phenotype-based assays were performed using cells and synthesis beads contained in small volumes of cell culture. These "nanodroplets" were generated either stochastically (see,

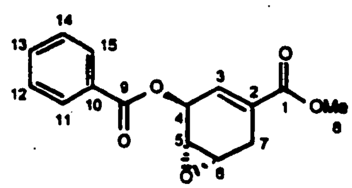
Borchardt et al. *Chem. Biol.* **1997**, *4*, 961) or on a molded, polydimethylsiloxane (PDMS) grid (You et al. *Chem. Biol.* **1997**, *4*, 969). Although these assays have yielded useful information, they suffer from several shortcomings, including the fact that the synthesis beads are not easily used more than once. Moreover, the synthesis described above was performed on 90 μm TentaGel beads, having a loading capacity of only approximately 80-100 picomolar equivalents per bead. In mink lung cell cytoblot assays searching for small molecule suppressors of trapoxin's and rapamycin's actions and using a subset of approximately 77,000 beads, these shortcomings manifested themselves in several ways, including the need for resynthesis of compounds corresponding to apparent positives. On the other hand, our early experience in screening these synthesis beads has revealed the ability to recover positive beads, cleave their EC-GC tags, and decode them successfully.

To address the problem noted above, colleagues at the Harvard Institute of Chemistry and Cell Biology have developed instrumentation and robotics that provide efficient arraying of synthesis beads into high density wells, releasing and transferring of compounds into high density stock solutions, and transferring of these solutions into high density PDMS assay plates. These assay plates are the preferred format for cytoblot assays (see, Stockwell et al. *Chem. Biol.* **1999**, *6*, 71), and the high density stock solutions are also well-suited for small molecule printing (with reference to provisional application number 60/133,595 entitled "Small Molecule Printing" filed May 11, 1999, the entire contents of which are incorporated herein by reference) To allow efficient release of compounds into storage wells without the need for removal of toxic byproducts, we have explored various linkers. To provide sufficient amounts of released compounds to allow their use in large numbers of assays, we have explored beads with higher loading capacities.

III. Specific Synthetic Procedures and Demonstration Compound Synthesis:

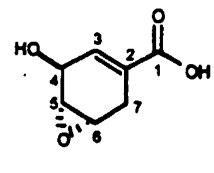
Shikimic acid, methyl ester (4) (Fischer et al. *Helv. Chim. Acta* **1934**, *17*, 1200). (–)-Shikimic acid, **3**, (Aldrich or Fluka, 7.0 g, 40.2 mmol, 1.0 equiv) and Amberlite IR-120(plus) resin (12.0 g, 22.8 mmol, 0.57 equiv) were combined in 210 mL MeOH. The mixture was refluxed with stirring for 36 h, cooled to rt, and filtered. The MeOH was evaporated to yield methyl ester **4** as a white solid (7.56 g, 100%) that was used without further purification. TLC: R_f 0.25 (9:1 CH_2Cl_2/MeOH). ^{1}H-NMR (400 MHz, CD_3OD): δ 6.78 (m, 1H), δ 4.36 (m, 1H), δ 3.98 (dt, 1H, J = 6.9, 5.3), δ 3.73 (s, 3H), δ 3.68 (dd, 1H, J = 7.1, 4.2), δ 2.68 (app ddt, 1H, J = 18.2, 4.9), δ 2.19 (app ddt, 1H, J = 18.2, 5.3). CI-MS (NH_3) m/z (rel int): 206 ($[M+NH_4]^+$, 100). HRMS (NH_3) m/z calcd for $C_8H_{16}NO_5$ 206.1029; found 206.1036.

(1*S*,5*R*,6*S*)-5-Hydroxy-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylic acid, methyl ester (5). Epoxycyclohexenol 5 was prepared by a modified version of the literature procedure (McGowan et al. *J. Org. Chem.* 1981, *46*, 2381) as follows: Shikimic acid, methyl ester, 4, (4.31 g, 22.9 mmol, 1.0 equiv) and triphenylphosphine (6.61 g, 25.2 mmol, 1.1 equiv) were dissolved in 100 mL THF and cooled to 0 °C in an ice bath. Diethylazodicarboxylate (3.97 mL, 25.2 mmol, 1.1 equiv) was dissolved in 10 mL THF and added dropwise with stirring via addition funnel. The mixture was stirred for 30 min at 0 °C, then warmed to rt and stirred for 1 h. The THF was evaporated and the residue was refluxed in 125 mL toluene for 90 min. The toluene was evaporated and the crude mixture was taken up in 100 mL hot Et_2O, cooled to rt, and filtered. This process was repeated with 100 mL Et_2O then 75 mL Et_2O. The crude product (8.22 g) was recovered as a brown residue that was determined by ^{1}H-NMR to consist of 53% desired epoxide 5, 26% triphenylphosphine oxide, and 21% bis(carboethoxy)hydrazine. The crude product (96% calculated yield) could be used without further purification or purified by silica flash chromatography (1:1 hexanes/EtOAc) to yield the pure product having analytical data consistent with the literature. TLC: R_f 0.16 (1:1 hexanes/EtOAc).

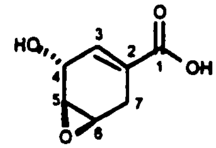


(1*S*,5*S*,6*S*)-5-Benzoyloxy-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylic acid, methyl ester (Benzoyl epoxycyclohexenol, methyl ester; 6). Epoxycyclohexenol 5 (4.75 g, 27.9 mmol, 1.0 equiv) was dissolved in 125 mL THF. Triphenylphosphine (13.18 g, 50.3 mmol, 1.8 equiv) and benzoic acid (6.14 g, 50.3 mmol, 1.8 equiv) were added and the solution was cooled to 0 °C in an ice bath. Diethylazodicarboxylate (7.9 mL, 50.3 mmol, 1.8 equiv) was added via syringe and the reaction was allowed to warm slowly to rt. After stirring overnight, the THF was evaporated and the crude mixture was taken up in 150 mL Et_2O and filtered twice to remove the triphenylphosphine oxide and bis(carboethoxy)hydrazine byproducts. The solvent was evaporated and the crude mixture was taken up in 100 mL Et_2O and again filtered twice. The crude product (17.8 g) was purified by silica gel flash chromatography (17:3 hexanes/EtOAc) to yield the pure benzoyl ester 6 as a clear, colorless oil (6.77 g, 88%). TLC: R_f 0.35 (3:1 hexanes/EtOAc). IR (film): 1718, 1669, 1246. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, 2H, J = 6.3, 3.3, C11-H, C15-H), 7.69 (t, 2H, J = 7.7, C12-H, C14-H), 7.59 (tt, 1H, J= 7.4, 1.4, C13-

H), 6.86 (ddd, 1H, J = 7.7, 2.9, 1.7, C3-H), 5.92 (app dt, 1H, J = 4.6, 2.0, 0.9, C4-H), 3.77 (s, 3H, C8-H_3), 3.51 (dd, 1H, J = 3.7, 2.8, C5-H), 3.41 (ddd, 1H, J = 4.5, 2.7, 1.7, C6-H), 3.05 (ddd, 1H, J = 20.0, 2.7, 1.3, C7-H_a), 2.76 (ddd, 1H, J = 20.0, 4.8, 2.7, C7-H_b). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.2, 165.3, 133.2, 129.7, 129.5, 129.4, 128.8, 128.2, 64.9, 51.8, 50.4, 50.1, 24.1. CI-MS (NH_3) *m/z* (rel int): 292 ([M+NH_4]$^+$, 100), 275 ([M+H]$^+$, 58). HRMS (NH_3) *m/z* calcd for $C_{15}H_{18}NO_5$ 292.1185; found 292.1179.



(+)-(1*S*,5*S*,6*S*)-5-Hydroxy-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylic acid ((+)-Epoxycyclohexenol carboxylic acid, (+)-7). Benzoyl epoxycyclohexenol methyl ester 6 (1.05 g, 3.84 mmol, 1.0 equiv) was dissolved in 40 mL THF and 10 mL H_2O and cooled to 0°C in an ice bath. Lithium hydroxide monohydrate (483 mg, 11.52 mmol, 3.0 equiv) was dissolved in 10 mL H_2O and added dropwise via addition funnel to the stirring reaction mixture. When the reaction was complete by TLC, the solution was acidified at 0 °C to pH 5 with Amberlite IR-120(plus) resin, filtered, and evaporated to yield the crude product as an off-white solid. NMR analysis indicated approximately 25% Payne rearrangement. Purification on silica gel (25:75:1 hexanes/EtOAc/AcOH, dry loaded from THF) afforded epoxycyclohexenol carboxylic acid (+)-7 as a white solid (352 mg, 59%). TLC: R_f 0.24 (25:75:1 hexanes/EtOAc/AcOH); R_f 0.49 (85:15:1 CH_2Cl_2/MeOH/AcOH). mp: 115.5-116.5°C. $[\alpha]_D^{23}$ = +57.6 (c 1.0, MeOH). IR (KBr pellet): 3700-2800, 1713, 1661, 1248. ^{1}H-NMR (500 MHz, CD_3CN): δ 6.67 (m, 1H, C3-H), 4.46 (m, 1H, C4-H), 3.36 (m, 1H, C6-H), 3.14 (m, 1H, C5-H), 2.76 (app dq, 1H, J = 19.8, 1.4, C7-H_α), 2.57 (app dq, 1H, J = 19.8, 2.4, C7-H_β). ^{1}H-NMR (400 MHz, CD_3OD): δ 6.73 (m, 1H, C3-H), 4.47 (m, 1H, C4-H), 3.41 (m, 1H, C6-H), 3.19 (m, 1H, C5-H), 2.81 (app dq, 1H, J = 19.8, 1.3, C7-H_α), 2.60 (app dq, 1H, J = 19.8, 2.5, C7-H_β). ^{13}C-NMR (125 MHz, CD_3CN): δ 168.6 (C1), 135.9 (C3), 127.0 (C2), 63.4 (C4), 53.6 (C5), 51.3 (C6), 25.1 (C7). ^{13}C-NMR (125 MHz, CD_3OD): δ 170.0 (C1), 135.4 (C3), 127.8 (C2), 63.7 (C4), 54.1 (C5), 51.9 (C6), 25.4 (C7). CI-MS (NH_3) *m/z* (rel int): 174 ([M+NH_4]$^+$, 66). HRMS (NH_3) *m/z* calcd for $C_7H_{12}NO_4$ 174.0766; found 174.0762.



(-)-(1*R*,5*R*,6*R*)-5-Hydroxy-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylic acid ((-)-Epoxycyclohexenol carboxylic acid, (–)-7). Epoxycyclohexenol, methyl ester 9 was prepared essentially as previously described (Wood et al. *J. Am. Chem. Soc.* **1990**, *112*, 8907) and recovered as a 1.6:1 mixture with the Payne rearranged isomer in 51% combined yield. This mixture (1.21 g, 7.15 mmol, 1.0 equiv) was dissolved in 14 mL 1:1 THF/H_2O and cooled to 0 °C in an ice bath. Lithium hydroxide (330 mg, 7.87 mmol, 1.1 equiv) in 3.3 mL H_2O was added dropwise over 10 min. The reaction was stirred at 0 °C until the starting material was consumed (approx 2 h, TLC: 25:75:1 hexanes/EtOAc/AcOH). The solution was acidified at 0 °C to pH 5 with Amberlyte IR-120(plus) resin, filtered, and evaporated to yield the crude product as a clear oil. Purification on silica gel (0-5% MeOH in CH_2Cl_2 gradient) afforded epoxycyclohexenol carboxylic acid (–)-7 as a white solid (477 mg, 43% based on mixture). TLC and ^{1}H-NMR identical to (+)-7 above. $[\alpha]_D^{23} = -50.6$ (*c* 1.0, MeOH). CI-MS (NH_3) *m/z* (rel int): 174 ($[M+NH_4]^+$, 75). HRMS (NH_3) *m/z* calcd for $C_7H_{12}NO_4$ 174.0766; found 174.0770.

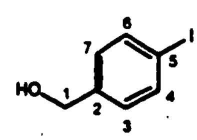
General Procedure for Synthesis of [[(Iodophenyl)methyl]oxidoimino]acetic acids (Iodobenzyl Nitrone Acids) (Keirs, D.; Overton, K. *Heterocycles* **1989**, *28*, 841). The appropriate *N*-(iodobenzyl)hydroxylamine (see Supporting Information, 1.0 equiv) and glyoxylic acid monohydrate (1.05 equiv) were dissolved in CH_2Cl_2 and stirred at rt until the reaction was complete by NMR (24 h). The reaction mixture was washed with 2 × H_2O and 1 × brine, dried ($MgSO_4$), filtered, and evaporated to yield the crude nitrone. The crude product was slurried in THF, then Et_2O was added with vigorous stirring. After trituration overnight, the pure nitrone carboxylic acid **11** was recovered by vacuum filtration in 47-67% yield.

[[(2-Iodophenyl)methyl]oxidoimino]acetic acid (2-Iodobenzyl nitrone acid, 11b). *N*-(2-Iodobenzyl)hydroxylamine (9.46 g, 38.0 mmol) was reacted in 250 mL CH_2Cl_2. The crude product was recovered as a slightly yellow solid (10.9 g) and slurried in 10 mL THF then 250 mL Et_2O. The pure product was recovered as white flakes (6.22 g, 54%). mp: 82 °C (dec). IR (film): 1715, 1470, 1414. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, 1H, *J* = 8.0, 1.0), 7.51 (dd, 1H, *J* = 7.6, 2.0), 7.48 (td, 1H, *J* = 7.4, 1.1), 7.44 (br s, 1H), 7.22 (s, 1H), 7.19 (ddd, 1H, *J* = 7.9, 7.2, 2.0), 5.21 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): 160.6, 140.5, 132.4, 132.3, 132.1, 130.5,

129.4, 101.0, 74.2. CI-MS (NH_3) *m/z* (rel int): 340 ($[M+2NH_3+H]^+$, 7), 323 ($[M+NH_4]^+$, 100), 306 ($[M+H]^+$, 10).

[[(3-Iodophenyl)methyl]oxid imino]acetic acid (3-Iodobenzyl nitrone acid, 11c). *N*-(3-Iodobenzyl)hydroxylamine (7.96 g, 32.0 mmol) was reacted in 250 mL CH_2Cl_2. After dilution with 250 mL CH_2Cl_2 and washing, the crude product was recovered as a slightly yellow solid (9.1 g) and slurried in 10 mL THF then 350 mL Et_2O. The pure product was recovered as white flakes (6.58 g, 68%). mp: 109.0-109.5°C (dec). IR (film): 1715, 1470, 1412. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84 (dt, 1H, *J* = 8.0, 1.3), 7.80 (t, 1H, *J* = 1.7), 7.63 (br s, 1H), 7.42 (dt, 1H, *J* = 7.7), 7.29 (s, 1H), 7.23 (t, 1H, *J* = 7.8), 5.00 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): 160.5, 139.4, 138.6, 131.8, 131.0, 130.0, 128.9, 94.9, 69.8. CI-MS (NH_3) *m/z* (rel int): 340 ($[M+2NH_3+H]^+$, 14), 323 ($[M+NH_4]^+$, 100), 306 ($[M+H]^+$, 4).

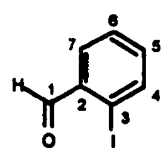
[[(4-Iodophenyl)methyl]oxidoimino]acetic acid (4-Iodobenzyl nitrone acid, 11d). *N*-(4-Iodobenzyl)hydroxylamine (11.8 g, 47.4 mmol) was reacted in 300 mL CH_2Cl_2. The crude product was recovered as a white powder (10.2 g) and slurried in 15 mL THF then 300 mL Et_2O. The pure product was recovered as a white powder (6.89 g, 48%). mp: 124.0 °C (dec, peach), 156-173 °C (dec, brown oil). IR (film): 1711, 1466, 1447, 1424, 1402. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.82 (d, 2H, *J* = 8.4), 7.27 (s, 1H), 7.17 (d, 2H, *J* = 8.3), 4.99 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): 160.5, 138.7, 131.4, 129.8, 129.2, 96.8, 70.2. EI-MS *m/z* (rel int): 305 (M^+, 2), 261 ($[M-CO_2]^+$, 6), 217 ($[M-HOOC-CH-NO]^+$, 100). FAB-MS (NBA/NaI) *m/z* (rel int): 328 ($[M+Na]^+$, 42), 306 ($[M+H]^+$, 25).



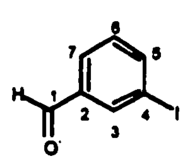
4-Iodobenzyl alcohol. (Acheson, R. M.; Lee, G. C. M. *J. Chem. Soc. Perkin Trans. I* **1987**, 2321-2332.) To a stirred suspension of sodium borohydride (5.68 g, 150 mmol, 2.0 equiv) in 50 mL dioxane at 0 °C was added dropwise a solution of 4-iodobenzoyl chloride (19.99 g, 75 mmol, 1.0 equiv) in 50 mL dioxane over 25 min. The resulting mixture was heated to 100 °C for 90 min under a reflux condenser then cooled to 0 °C. 50 mL H_2O was added cautiously under a flowing stream of nitrogen. **[CAUTION: Evolves gas!]** The mixture was extracted 3 × 125 mL CH_2Cl_2 and the combined organic extracts were washed with 2 × H_2O, 2 × 0.1N HCl, 2 × 1N NaOH, H_2O, and brine, dried ($MgSO_4$), filtered, and evaporated to yield 16.9 g of crude 4-iodobenzyl alcohol as a white solid, determined by NMR to contain 78% desired product with

the remainder residual starting material and 4-iodobenzoic acid. The crude product was used without further purification. mp: 61.0-66.5°C. TLC R_f: 0.27 (3:1 hexanes/EtOAc). IR (film): 3306, 1005, 791. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 (d, 2H, J = 8.3, C4-H, C6-H), 7.12 (d, 2H, J = 8.5, C3-H, C7-H), 4.66 (br d, 2H, J = 4.1, C1-H_2), 1.67 (br t, 1H, C1-OH). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 140.4, 137.6, 128.8, 93.0, 64.6. EI-MS m/z (rel int): 234 (M^+, 100).

General Procedure for Synthesis of Iodobenzaldehydes. (Acheson, R. M.; Lee, G. C. M. *J. Chem. Soc. Perkin Trans. I* **1987**, 2321-2332.) To a stirred suspension of pyridinium dichromate (1.5 equiv) in CH_2Cl_2 was added the appropriate iodobenzyl alcohol (1.0 equiv) at rt. The mixture was stirred vigorously for 20-40 h until the reaction was complete by TLC. Et_2O was added and the mixture was filtered through a column of 2" celite over 2" silica gel. Elution of the product with additional Et_2O and evaporation of solvents yielded the crude iodobenzaldehyde which was approximately 95% pure by ^{1}H-NMR and used without further purification.

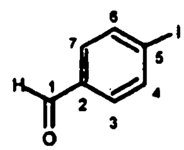


2-Iodobenzaldehyde. Commercially available 2-iodobenzyl alcohol (10.0 g, 42.7 mmol) was dissolved in 200 mL CH_2Cl_2. Upon completion, the reaction was diluted with 250 mL Et_2O. The product was recovered as a brown liquid (10.3 g, 104%). TLC: R_f 0.57 (3:1 hexanes/EtOAc). IR (neat): 3061, 2853, 2745, 1696, 1580, 1561. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H, C1-H), 7.95 (dd, 1H, J = 7.9, 1.0, C4-H), 7.88 (dd, 1H, J = 7.7, 1.8, C7-H), 7.47 (td, 1H, J = 7.5 0.8, C6-H), 7.29 (td, 1H, J = 7.6, 1.8, C5-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 195.1, 140.2, 135.1, 134.7, 129.9, 128.4, 100.5. EI-MS m/z (rel int): 232 (M^+, 100), 231 ($[M-H]^+$, 40), 203 ($[M-CHO]^+$, 15), 105 ($[M-I]^+$, 3).



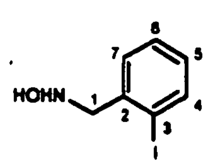
3-Iodobenzaldehyde. Commercially available 3-iodobenzyl alcohol (5.32 mL, 41.9 mmol) was dissolved in 200 mL CH_2Cl_2. Upon completion, the reaction was diluted with 250 mL Et_2O. The product was recovered as off-white crystals (8.1 g, 83.4%) mp: 48.0-55.0°C. TLC: R_f 0.54 (3:1 hexanes/EtOAc). IR (neat): 3058, 2824, 2728, 1698, 1586, 1566. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H, C1-H), 8.22 (t, 1H, J = 1.6, C3-H), 7.96 (dt, 1H, J = 7.7, 1.4,

C5-H), 7.85 (dt, 1H, J = 7.7, 1.3, C7-H), 7.29 (t, 1H, J = 7.7, C6-H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 190.6, 143.1, 138.4, 138.0, 130.7, 128.8, 94.6. EI-MS m/z (rel int): 232 (M^+, 100), 231 ($[M-H]^+$, 25), 203 ($[M-CHO]^+$, 14), 104 ($[M-HI]^+$, 38).

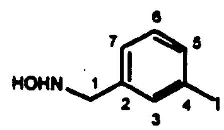


4-Iodobenzaldehyde. 4-Iodobenzyl alcohol prepared above (16.9 g, 72.2 mmol) was dissolved in 350 mL CH_2Cl_2. Upon completion, the reaction was diluted with 250 mL Et_2O. The product was recovered as a white solid (13.7 g, 81.8%) mp: 71.0-73.5°C. TLC: R_f 0.50 (3:1 hexanes/EtOAc). IR (film): 2820, 2726, 1690, 1584, 1564, 804. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H, C1-H), 7.92 (d, 2H, J = 8.5, C4-H, C6-H), 7.59 (d, 2H, J = 8.1, C3-H, C7-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 191.4, 138.4, 135.6, 130.8, 102.8. EI-MS m/z (rel int): 232 (M^+, 100), 203 ($[M-CHO]^+$, 24).

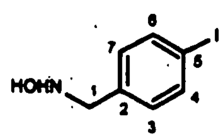
General Procedure for Synthesis of *N*-(Iodobenzyl)hydroxylamines. (Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897-2904.) To a stirred solution of the appropriate iodobenzaldehyde (1.0 equiv) in a mixture of MeOH and THF was added a trace of Methyl Orange at rt. Hydroxylamine hydrochloride (1.25 equiv) was dissolved in H_2O and added to the iodobenzaldehyde solution. The pH was raised to 9 with 6N KOH and additional THF, MeOH, and/or H_2O were added to form a homogeneous solution. Solid sodium cyanoborohydride (1.0 equiv) was added and 2N HCl in aq MeOH was added via addition funnel until the solution was ruby red. **[CAUTION: Evolves gas!]** Additional acid was added as necessary to maintain the color during the reaction. After the reaction was complete by NMR (15-20 h), the bulk of the MeOH and THF were evaporated. The remaining aq solution was adjusted to pH 12 with 6N KOH and extracted with 4 × CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered, and evaporated to yield the crude *N*-(iodobenzyl)hydroxylamine which was determined by NMR to contain 90-94% of the desired product with the remainder *N,N*-bis(iodobenzyl)hydroxylamine. The crude product was used without further purification.



***N*-(2-Iodobenzyl)hydroxylamine.** 2-Iodobenzaldehyde prepared above (10.3 g, 44.4 mmol) was dissolved in 50 mL MeOH and 10 mL THF. After addition of $H_2NOH{\bullet}HCl$ (10 mL H_2O) and 6N KOH, an additional 50 mL THF, 30 mL H_2O, and 30 mL MeOH were added. The product was recovered as a cloudy orange oil (9.46 g, 85.6%, 90% desired product). IR (film): 3256, 3057, 2872, 1564, 1466, 1435, 1013, 748. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, 1H, J = 7.8, 1.2, C4-H), 7.58 (dd, 1H, J = 7.4, 1.8, C7-H), 7.34 (td, 1H, J = 7.4, 1.2, C6-H), 7.00 (td, 1H, J = 7.6, 1.8, C5-H), 5.5 (br s, 1H, C1-NHOH), 5.0 (br s, 1H, C1-NHOH), 4.13 (s, 2H, C1-H_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.5, 139.1, 131.0, 129.4, 128.3, 100.1, 62.0. EI-MS *m/z* (rel int): 249 (M^+, 36), 217 ($[M\text{-}NHOH]^+$, 100), 122 ($[M\text{-}I]^+$, 30). CI-MS (NH_3) *m/z* (rel int): 284 ([M+2NH_3+H]+, 30), 267 ($[M+NH_4]^+$, 100), 250 ($[M+H]^+$, 27).



***N*-(3-Iodobenzyl)hydroxylamine.** 3-Iodobenzaldehyde prepared above (8.1 g, 34.9 mmol) was dissolved in 50 mL MeOH and 20 mL THF. After addition of $H_2NOH{\bullet}HCl$ (10 mL H_2O) and 6N KOH, an additional 20 mL H_2O, 10 mL THF, and 10 mL MeOH were added. The product was recovered as a white solid (7.96 g, 91.6%, 92% desired product). mp: 63.0-70.0°C. IR (film): 3256, 3056, 2857, 1591, 1564, 1470, 1420, 1063, 995, 777. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (t, 1H, J = 1.6, C6-H), 7.63 (dt, 1H, J = 7.9, 1.3, C5-H), 7.31 (dt, 1H, J = 7.6, C7-H), 7.09 (t, 1H, J = 7.8, C6-H), 5.5 (br s, 1H, C1-NHOH), 5.1 (br s, 1H, C1-NHOH), 3.98 (s, 2H, C1-H_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.9, 137.9, 136.6, 130.2, 128.2, 94.4, 57.4. EI-MS *m/z* (rel int): 249 (M^+, 65), 217 ($[M\text{-}NHOH]^+$, 100). CI-MS (NH_3) *m/z* (rel int): 284 ([M+2NH_3+H]+, 28), 267 ($[M+NH_4]^+$, 100), 250 ($[M+H]^+$, 45).



***N*-(4-Iodobenzyl)hydroxylamine.** 4-Iodobenzaldehyde prepared above (13.7 g, 59.0 mmol) was dissolved in 80 mL MeOH and 60 mL THF. After addition of $H_2NOH{\bullet}HCl$ (10 mL H_2O) and 6N KOH, an additional 30 mL H_2O was added. The product was recovered as a white solid (11.8 g, 80.3%, 94% desired product). mp: 89.0-95.0°C. IR (film): 3245, 3173, 2916, 2847, 1483, 1007, 787. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.66 (d, 2H, J = 8.3, C4-H, C6-H), 7.06 (d, 2H, J = 8.3, C3-H, C7-H), 5.4-4.7 (br s, 2H, C1-NHOH), 3.90 (s, 2H, C1-H_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 137.6, 137.4, 131.0, 93.2, 57.4. EI-MS *m/z* (rel int): 249 (M^+, 29), 217

([M-NHOH]$^+$, 100). CI-MS (NH_3) *m/z* (rel int): 267 ([M+NH_4]$^+$, 40), 250 ([M+H]$^+$, 100), 234 ([M-NHOH+NH_3]$^+$, 52), 217 ([M-NHOH]$^+$, 63).

Demonstration Compounds – General. For demonstration compound photocleavage reactions, 50 mg of resin was divided between two 500 μL Eppendorf tubes, suspended in 450 μL CH_3CN each, and photolyzed for 2 h. Trace impurities resulting only from the photocleavage reaction were identified by photolysis of underivatized 3-amino-3-*o*-nitrophenylpropionic acid (Anp)-loaded resin (see below) and discounted in purity calculations.

Identification of Photolysis Byproducts. 50 mg of underivatized H_2N-Anp-Tentagel resin was photolyzed and analyzed by TLC, HPLC, ^{1}H-NMR and FAB-MS as follows: TLC (trace amounts, detectable by UV only): R_f 0.55 (9:1 CH_2Cl_2/MeOH); R_f 0.71, 0.82 (1:1 CH_2Cl_2/THF); R_f 0.47, 0.71 (4:1 CH_2Cl_2/THF); R_f 0.18, 0.63 (1:1 CH_2Cl_2/EtOAc). HPLC (trace amounts): t_R = 2.073 min, λ_{max} = 217, 244, 303 nm; t_R = 2.462 min, λ_{max} = 242, 301 nm; t_R = 2.980 min, λ_{max} = 243 nm; t_R = 3.141 min, λ_{max} = 239 nm. ^{1}H-NMR (500 MHz, CD_3CN, trace amounts except for PEG): δ 7.70 (dd, *J* = 5.6, 3.3), 7.60 (obs md, *J* = 5.9, 2.5), 7.57 (td, *J* = 7.8, 1.3), 7.52 (d, *J* = 7.4), 7.09 (td, *J* = 7.5, 0.8), 6.95 (d, *J* = 7.9), 4.44 (br s), 4.30 (q, *J* = 7.1), 4.22 (m), 3.55 (s, PEG), 2.85-2.50 (br), 1.31 (t, *J* = 7.1), 1.26 (br s). FAB-MS (glycerol) *m/z* (rel int): 503 ([M+H]$^+$, 2). FAB-MS (NBA/NaI) *m/z* (rel int): 569 ([M+Na]$^+$, 100), 547 ([M+H]$^+$, 13), 553 ([M+Na]$^+$, 58), 531 ([M+H]$^+$, 25). Dibutylphthalate was occasionally detected by HPLC and LC-MS (HPLC: t_R = 3.30 min; LC-MS: t_R = 5.0 min, [M+H]$^+$ = 279). HPLC analysis also showed varying amounts of a secondary peak which trailed each product by 0.3-0.4 min and was highly UV active at 254 and 280 nm. This impurity could not be identified by LC-MS but might result form product cleavage at polyethyleneglycol rather than at the Anp linker. Adventitious oxidation of polyethyleneglycol to labile peroxides or esters has been discussed in the literature (Rapp Polymere Home Page. http://www.rapp-polymere.com (accessed June 1999).

3-Amino-3-(2-nitrophenyl)propionic acid (H-Anp-OH). The photolinker was synthesized as the free amino acid by a modified version of the literature procedure (Brown et al. *Mol. Div.* **1995**, *1*, 4) as follows: 2-Nitrobenzaldehyde (20.0 g, 132 mmol, 1.0 equiv) and malonic acid (17.8 g, 171 mmol, 1.3 equiv) were slurried in 20 mL glacial acetic acid (AcOH) and warmed to 45 °C with stirring. Solid ammonium acetate (25.0 g, 324 mmol, 2.5 equiv) was added in one portion and the mixture heated to 60 °C to form a brown solution. After 15 min, a brown solid precipitated and was broken up with a spatula. 15 mL AcOH was added and the mixture stirred for an additional 45 min at 60 °C. Another 15 mL AcOH was added and the mixture was heated to 98-100 °C and stirred for 3 h, eventually forming a deep red solution. 70

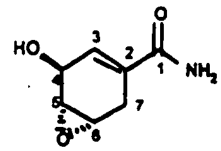
mL concd HCl was added and the solution was stirred for another 1 h at 98-100 °C. The solution was cooled to rt, diluted with 150 mL H_2O, and washed with 200 mL Et_2O. The aqueous layer was adjusted to pH 4.5, resulting in formation of a precipitate. The solids were collected by filtration and washed with Et_2O to yield H-Anp-OH as a yellow solid (18.3 g, 66%) exhibiting satisfactory analytical data.

***N*-(9-Fluorenylmethyloxycarbonyl)-3-Amino-3-(2-nitrophenyl)propionic acid (Fmoc-Anp-OH).** The Fmoc-protected photolinker was synthesized by a modified version of the literature procedure (Brown et al. *Mol. Div.* **1995**, *1*, 4) as follows: H-Anp-OH (5 g, 23.8 mmol, 1.0 equiv), *N*-(9-fluorenylmethyloxycarbonyloxy)succinimide (Fmoc-OSu, 8.8 g, 26.1 mmol, 1.1 equiv) and 0.85M aq sodium carbonate (100 mL, 85 mmol, 3.5 equiv) were combined in 150 mL THF and stirred for 90 min. The reaction mixture was washed with 2 × 100 mL hexanes, acidified to pH 6, and extracted with 3 × 150 mL EtOAc. The combined organic layers were washed with 2 × 1N HCl, 1 × H_2O, 1 × brine, dried ($MgSO_4$), filtered, and evaporated to yield the crude product as a light brown solid. The solid was taken up in 250 mL hot EtOAc and filtered hot. Hexanes were added until precipitate began to form and the mixture was allowed to cool to rt overnight. The desired product (5.5 g) was recovered by filtration as an off-white solid having analytical data consistent with the literature. A second crop of product (0.85 g) was recovered for a combined yield of 62%.

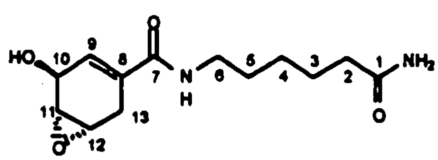
H_2N-Anp-TentaGel Resin (36R, 37a-cR). TentaGel S NH_2 (10.0 g, 0.29 meq/g, 2.9 mmol, 1.0 equiv) was placed in a 100 mL fritted glass tube and swollen in distd THF with N_2 bubbling for 2 min. The vessel was drained and the resin was swollen in distd CH_2Cl_2 for another 2 min. The vessel was drained and Fmoc-Anp-OH (1.881 g, 4.35 mmol, 1.5 equiv), HATU (1.654 g, 4.35 mmol, 1.5 equiv), NMP (50 mL), and DIPEA (1.52 mL, 8.70 mmol, 3.0 equiv) were added in sequence. The reaction was allowed to proceed for 5 h. The resin was washed with 4 × NMP and 4 × CH_2Cl_2 to yield Fmoc-Anp-TentaGel which was negative to Kaiser ninhydrin test. The Fmoc group was removed by 2 × 15 min treatments with 50 mL of freshly prepared 20% piperidine in DMF. The resin was washed as above to yield H_2N-Anp-TentaGel resin, **36R, 37a-cR** (10.6 g, 100% by mass) which turned brown after heating for 2 min under Kaiser conditions.

H_2N-Aca-Anp-TentaGel Resin (37d-fR). H_2N-Anp-TentaGel resin, **36R**, (3.18 g, 0.27 meq/g, 0.873 mmol, 1.0 equiv) was placed in a 50 mL fritted glass tube and swollen in distd CH_2Cl_2 for 2 min. The vessel was drained and *N*-Fmoc-ω-Aminocaproic acid (Fmoc-Aca-OH, 925.6 mg, 2.619 mmol, 3.0 equiv), PyBOP (1.363 g, 2.619 mmol, 3.0 equiv), 30 mL NMP, and DIPEA (0.760 mL, 4.365 mmol, 5.0 equiv) were added in sequence. After 1 h, the resin was

washed as above to yield Fmoc-Aca-Anp-TentaGel resin which was negative to Kaiser test. Fmoc deprotection as above yielded H_2N-Aca-Anp-TentaGel resin, **37d-fR** (3.24 g, 99% by mass) which was positive to Kaiser test.



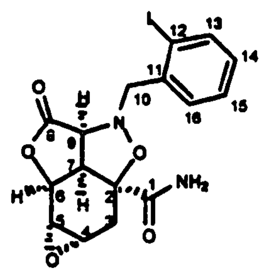
(1*S*,5*S*,6*S*)-5-Hydroxy-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxamide (Epoxycyclohexenol carboxamide, 38a-c). H_2N-Anp-TentaGel resin, **37a-cR** (1.59 g, 0.27 meq/g, 0.436 mmol, 1.0 equiv) was placed in a 50 mL fritted glass tube. Epoxycyclohexenol carboxylic acid (+)-**7** (74.9 mg, 0.480 mmol, 1.1 equiv), PyBOP (249.8 mg, 0.480 mmol, 1.1 equiv), 20 mL NMP, and DIPEA (228 μL, 1.309 mmol, 3.0 equiv) were added in sequence. After 2 h, the resin was washed as above to yield Epoxycyclohexenol-Anp-TentaGel resin **38a-cR** (1.6343 g, 99% by mass) which was negative to Kaiser test. Photolysis of the resin yielded the crude epoxycyclohexenol carboxamide, **38a-c**, as a yellow oil. TLC: R_f 0.18 (9:1 CH_2Cl_2/MeOH); R_f 0.11 (1:1 CH_2Cl_2/THF). HPLC: $t_R = 0.306$ min, $\lambda_{max} = 215$ nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 6.28 (m, 1H, C3-H), 4.42 (m, 1H, C4-H), 3.35 (m, 1H, C5-H), 3.13 (m, 1H, C6-H), 2.73 (ddq, 1H, J = 4.0, 1.3, C7-H_a), 2.59 (app dq, 1H, J = 7.3, 2.5, C7-H_b). CI-MS (NH_3) *m/z* (rel int): 173 ($[M+NH^4]^+$, 90), 156 ($[M+H]^+$, 33). HRMS (NH_3) *m/z* calcd for $C_7H_{13}N_2O_3$ 173.0926; found 173.0929



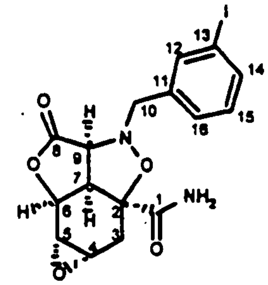
(1*S*,5*S*,6*S*)-*N*-(6-amino-6-oxohexyl)-5-hydroxy-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxamide (Epoxycyclohexenol ω-amino caproic carboxamide, 38d-f). Epoxycyclohexenol-Aca-Anp-TentaGel resin **38d-fR** was synthesized essentially as above from H_2N-Aca-Anp-TentaGel resin, **37d-fR** (97% yield by mass). Photolysis of the resin yielded the crude epoxycyclohexenol carboxamide, **38d-f**, as a yellow oil. TLC: R_f 0.09 (9:1 CH_2Cl_2/MeOH); R_f 0.03 (1:1 CH_2Cl_2/THF). HPLC: $t_R = 1.717$ min, $\lambda_{max} = 203, 211$ nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 6.60 (br s, 1H, C7-NH), 6.20 (m, 1H, C9-H), 6.04 (br s, 1H, C1-NH_a), 5.51 (br s, 1H, C1-NH_b), 4.41 (m, 1H, C10-H), 3.35 (m, 1H, C11-H), 3.17 (q, 2H, J = 6.8, C6-H_2), 3.14 (m, 1H, C12-H), 2.72 (app ddd, 1H, J = 19.8, 2.7, 1.3, C13-H_a), 2.58 (app dq, 1H, J = 19.6, 2.4, C13-H_b), 2.11 (t, 2H, J = 7.5, C2-H_2), 1.54 (quint, 2H, J = 7.6, C5-H_2), 1.47 (quint, 2H, J = 7.3, C3-H_2), 1.29 (m, 2H, C4-H_2). FAB-MS (NBA/NaI) *m/z* (rel int): 291 ($[M+Na]^+$,

100), 269 ($[M+H]^+$, 22). HRMS (NBA/NaI) *m/z* calcd for $C_{13}H_{20}N_2O_4Na$ 291.1321; found 291.1320.

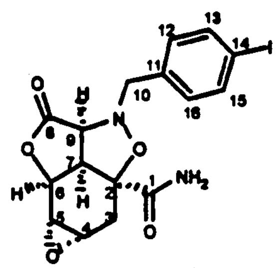
General Procedure for Tandem Acylation-1,3-Dipolar Cycloaddition Reaction. In a PD-10 column were placed the appropriate epoxycyclohexenol resin, **38R** (533 mg, 0.26 meq/g, 133.9 μmol, 1.0 equiv), PyBroP (127.6 mg, 273.8 μmol, 2.0 equiv), and the appropriate iodobenzyl nitrone acid, **11** (83.5 mg, 273.8 μmol, 2.0 equiv). CH_2Cl_2 (5.3 mL) was added and the tube was flushed with Ar, capped, vortexed briefly, and immediately cooled to 0 °C in an ice bath. DIPEA (95.4 μL, 547.5 μmol, 4.0 equiv) was added and the tube was vortexed briefly and returned to 0 °C. DMAP (18.4 mg, 150.6 μmol, 1.1 equiv) was added as 97.4 μL of a CH_2Cl_2 stock solution and the tube was vortexed briefly and returned to 0 °C for 10 min. The tube was then wrapped with parafilm, wrapped in foil, and transferred to a Labquake in a 4 °C cold cabinet. After mixing overnight, the resin was washed (Method B) and exposed to the coupling conditions twice more to yield the iodobenzyl tetracycle resin, **39R**. Photolysis of the resin yielded the crude iodobenzyl tetracycle, **39**, as a yellow oil.



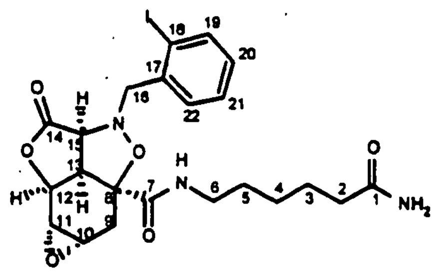
[2aS-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-Hexahydro-3-[(2-iodophenyl)methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (2-Iodobenzyl tetracycle carboxamide, 39a). TLC: R_f 0.38 (4:1 CH_2Cl_2/THF); R_f 0.27 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 2.573 min, λ_{max} = 202, 230 nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 7.87 (dd, 1H, J = 7.9, 1.2, C13-H), 7.52 (dd, 1H, J = 7.8, 1.7, C16-H), 7.38 (td, 1H, J = 7.5, 1.2, C15-H), 7.04 (td, 1H, J = 7.5, 1.8, C14-H), 6.06 (br s, 1H, C1-NH_a), 5.51 (br s, 1H, C1-NH_b), 5.12 (dd, 1H, J = 7.2, 2.7, C6-H), 4.38 (d, 1H, J = 8.2, C9-H), 4.35 (d, 1H, J = 14.6, C10-H_a), 4.09 (d, 1H, J = 14.6, C10-H_b), 3.87 (t, 1H, J = 7.5, C7-H), 3.51 (dd, 1H, J = 3.6, 2.7, C5-H), 3.30 (dd, 1H, J = 6.2, 2.4, C4-H), 2.34 (dd, 1H, J = 16.8, 1.7, C3-H_a), 2.25 (dd, 1H, J = 16.8, 2.7, C3-H_b). FAB-MS (glycerol) *m/z* (rel int): 443 ($[M+H]^+$, 42). HRMS (glycerol) *m/z* calcd for $C_{16}H_{16}IN_2O_5$ 443.0104; found 443.0110.



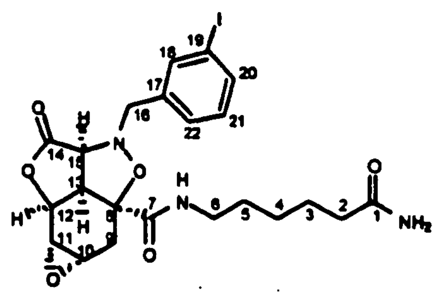
[2aS-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-Hexahydro-3-[(3-iodophenyl)methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (3-Iodobenzyl tetracycle carboxamide, 39b). TLC: R_f 0.38 (4:1 CH_2Cl_2/THF); R_f 0.30 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 2.893 min, λ_{max} = 203, 229 nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 7.77 (app d, 1H, J = 1.6, C12-H), 7.65 (dd, 1H, J = 7.8, 1.4, C14-H), 7.37 (dd, 1H, J = 7.7, 1.0, C16-H), 7.12 (t, 1H, J = 7.8, C15-H), 6.09 (br s, 1H, C1-NH_a), 5.70 (br s, 1H, C1-NH_b), 5.09 (dd, 1H, J = 7.2, 2.6, C6-H), 4.32 (d, 1H, J = 8.2, C9-H), 4.26 (d, 1H, J = 14.2, C10-H_a), 3.95 (d, 1H, J = 14.2, C10-H_b), 3.86 (t, 1H, J = 7.5, C7-H), 3.49 (dd, 1H, J = 3.6, 2.7, C5-H), 3.28 (dd, 1H, J = 6.2, 2.3, C4-H), 2.34 (dd, 1H, J = 16.8, 1.7, C3-H_a), 2.25 (dd, 1H, J = 16.8, 2.7, C3-H_b). FAB-MS (glycerol) *m/z* (rel int): 443 ($[M+H]^+$, 38). HRMS (glycerol) *m/z* calcd for $C_{16}H_{16}IN_2O_5$ 443.0104; found 443.0105.



[2aS-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-Hexahydro-3-[(4-iodophenyl)methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (4-Iodobenzyl tetracycle carboxamide, 39c). TLC: R_f 0.38 (4:1 CH_2Cl_2/THF); R_f 0..27 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 2.898 min, λ_{max} = 202, 234 nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 7.69 (d, 2H, J = 8.3, C13-H, C15-H), 7.17 (d, 2H, J = 8.3, C12-H, C16-H), 6.06 (br s , 1H, C1-NH_a), 5.65 (br s, 1H, C1-NH_b), 5.09 (dd, 1H, J = 7.3, 2.6, C6-H), 4.32 (d, 1H, J = 8.2, C9-H), 4.24 (d, 1H, J = 14.1, C10-H_a), 3.95 (d, 1H, J = 14.1, C10-H_b), 3.85 (t, 1H, J = 7.5, C7-H), 3.49 (dd, 1H, J = 3.6, 2.7, C5-H), 3.28 (dd, 1H, J = 6.2, 2.4, C4-H), 2.34 (dd, 1H, J = 16.8, 1.7, C3-H_a), 2.23 (dd, 1H, J = 16.8, 2.7, C3-H_b). FAB-MS (glycerol) *m/z* (rel int): 443 ($[M+H]^+$, 28). HRMS (glycerol) *m/z* calcd for $C_{16}H_{16}IN_2O_5$ 443.0104; found 443.0102.

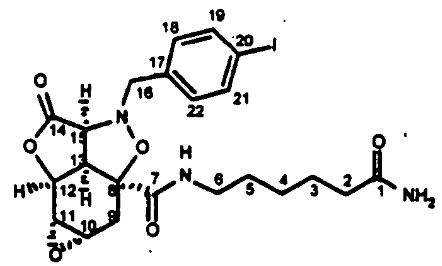


[2a*S*-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-*N*-(6-Amino-6-oxohexyl)hexahydro-3-[(2-iodophenyl)methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (2-Iodobenzyl tetracycle ω-aminocaproic carboxamide, 39d). TLC: R_f 0.42 (9:1 CH_2Cl_2/MeOH); R_f 0.14 (1:1 CH_2Cl_2/THF). HPLC: t_R = 2.894 min, λ_{max} = 202, 229 nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 7.89 (dd, 1H, J = 7.9, 1.2, C19-H), 7.48 (dd, 1H, J = 8.3, 2.3, C22-H), 7.40 (td, 1H, J = 7.5, 1.2, C21-H), 7.05 (td, 1H, J = 7.6, 1.8, C20-H), 6.11 (br s, 1H, C7-NH), 6.02 (br s, 1H; C1-NH_a), 5.50 (br s, 1H, C1-NH_b), 5.11 (dd, 1H, J = 7.2, 2.7, C12-H), 4.39 (d, 1H, J = 8.2, C15-H), 4.33 (d, 1H, J = 14.7, C16-H_a), 4.07 (d, 1H, J = 14.6, C16-H_b), 3.86 (t, 1H, J = 7.7, C13-H), 3.50 (dd, 1H, J = 3.6, 2.7, C11-H), 3.29 (dd, 1H, J = 6.3, 2.5, C10-H), 3.02 (m, 1H, C6-H_a), 2.85 (m, 1H, C6-H_b), 2.31 (dd, 1H, J = 16.6, 1.9, C9-H_a), 2.21 (dd, 1H, J = 16.8, 2.7, C9-H_b), 2.07 (t, 2H, J = 7.5, C2-H_2), 1.46 (m, 2H, C3-H_2), 1.26 (m, 2H, C5-H_2), 1.14 (m, 2H, C4-H_2). FAB-MS (glycerol) *m/z* (rel int): 556 ([M+H]$^+$, 33). HRMS (glycerol) *m/z* calcd for $C_{22}H_{27}IN_3O_6$ 556.0945; found 556.0957.



[2a*S*-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-*N*-(6-Amino-6-oxohexyl)hexahydro-3-[(3-iodophenyl)methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (3-Iodobenzyl tetracycle ω-aminocaproic carboxamide, 39e). TLC: R_f 0.38 (9:1 CH_2Cl_2/MeOH); R_f 0.15 (1:1 CH_2Cl_2/THF). HPLC: t_R = 2.962 min, λ_{max} = 207, 229 nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 7.75 (app d, 1H, J = 1.4, C18-H), 7.67 (dd, 1H J = 7.9, 1.2, C20-H), 7.37 (dd, 1H, J = 7.7, 1.0, C22-H), 7.14 (t, 1H, J = 7.8, C21-H), 6.25 (br s, 1H, C7-NH), 6.02 (br s, 1H, C1-NH_a), 5.50 (br s, 1H, C1-NH_b), 5.09 (dd, 1H, J = 7.3, 2.6, C12-H), 4.34 (d, 1H, J = 8.2, C15-H), 4.24 (d, 1H, J = 14.2, C16-H_a), 3.94 (d, 1H, J = 14.2, C16-H_b), 3.84 (t, 1H, J = 7.7, C13-H), 3.49 (dd, 1H, J = 3.6, 2.7, C11-H), 3.28 (dd, 1H, J = 6.0, 2.6, C10-H), 3.07 (m,

1H, C6-H_a), 2.96 (m, 1H, C6-H_b), 2.28 (dd, 1H, J = 16.8, 1.9, C9-H_a), 2.21 (dd, 1H, J = 16.8, 2.8, C9-H_b), 2.08 (t, 2H, J = 7.5, C2-H2), 1.50 (m, 2H, C3-H2), 1.26 (m, 2H, C5-H2), 1.18 (m, 2H, C4-H2). FAB-MS (glycerol) m/z (rel int): 556 ([M+H]+, 100). HRMS (glycerol) m/z calcd for $C_{22}H_{27}IN_3O_6$ 556.0945; found 556.0953.

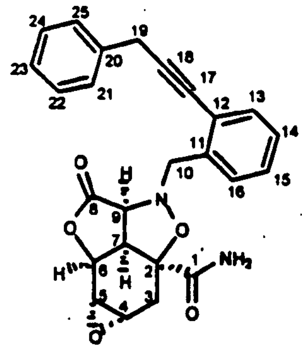


[2a*S*-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-*N*-(6-Amino-6-oxohexyl)hexahydro-3-[(4-iodophenyl)methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (4-Iodobenzyl tetracycle ω-aminocaproic carboxamide, 39f). TLC: R_f 0.32 (9:1 CH_2Cl_2/MeOH); R_f 0.15 (1:1 THF/CH_2Cl_2). HPLC: t_R = 2.974 min, λ_{max} = 204, 234 nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 7.71 (d, 2H, J = 8.3, C19-H, C21-H), 7.15 (d, 2H, J = 8.3, C18-H, C22-H), 6.21 (br s, 1H, C7-NH), 6.02 (br s, 1H, C1-NH_a, 5.51 (br s, 1H, C1-NH_b), 5.08 (dd, 1H, J = 7.2, 2.6, C12-H), 4.32 (d, 1H, J = 8.2, C15-H), 4.22 (d, 1H, J = 14.1, C16-H_a), 3.94 (d, 1H, J = 14.1, C16-H_b), 3.83 (t, 1H, J = 7.7, C13-H), 3.49 (dd, 1H, J = 3.6, 2.7, C11-H), 3.27 (dd, 1H, J = 6.2, 2.4, C10-H), 3.03 (m, 1H, C6-H_a), 2.92 (m, 1H, C6-H_b), 2.28 (m, 1H, C9-H_a), 2.20 (m, 1H, C9-H_b), 2.09 (t, 2H, J = 7.7, C2-H_2), 1.5 (m, 2H, C3-H_2), 1.3-1.1 (m, 4H, C5-H_2, C4-H_2). FAB-MS (glycerol) *m/z* (rel int): 556 ($[M+H]^+$, 100). HRMS (glycerol) *m/z* calcd for $C_{22}H_{27}IN_3O_6$ 556.0945; found 556.0947.

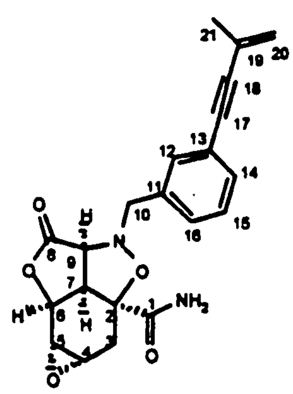
General Procedure for Sonogashira/Castro-Stephens Alkyne Coupling Reaction. To 50 mg (10.5 μmol) of the appropriate iodobenzyl tetracycle resin, **39R**, in a 2 mL Bio-Spin® column was added copper(I) iodide (4.4 mg, 23.1 μmol, 2.2 equiv) and bis(triphenylphosphine)palladium(II) chloride (8.1 mg, 11.55 μmol, 1.1 equiv). DMF (500 μL) was added and the tube was flushed with Ar, capped, and shaken to dissolve the reagents. DIPEA (54.9 μL, 315 μmol, 30 equiv) and the appropriate alkyne (20 equiv) were added and the tube was capped, shaken, wrapped with parafilm, and wrapped in foil. After mixing at rt (*para*: 15 min, *meta*: 30 min, *ortho*: 45 min), the resin was washed (Method A) and dried under vacuum. Photolysis of the resin, **40R**, yielded the crude alkynylbenzyl tetracycle, **40**, as a yellow oil.

General Procedure f r Sonogashira/Castro-Stephens Alkyne Coupling Reaction with Bis(Terminal Alkynes). The same procedure was used as above except $(Ph_3P)_2PdCl_2$ was

replaced with tetrakis(triphenylphosphine)palladium(0) (prepared as previously described) (Coulson, D.L. *Inorg. Synth.* **1972**, *13*, 121) and 70 equiv of DIPEA and 50 equiv of alkyne were used.

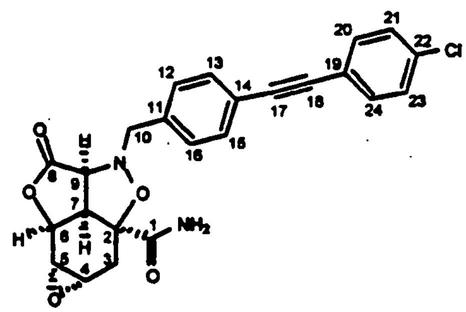


[2aS-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-Hexahydro-3-[[2-(3-phenyl-1-propynyl)phenyl]methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (*o*-(3-Phenyl-1-propynyl)benzyl Tetracycle Carboxamide, 40a). TLC: R_f 0.44 (4:1 CH_2Cl_2/THF); R_f 0.30 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.114 min, λ_{max} = (203), 208, 246 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.50 (d, 1H, J = 7.4, C13-H), 7.44 (d, 1H, J = 7.4, C16-H), 7.43 (obs d, 2H, C21-H, C25-H), 7.36 (t, 2H, J = 7.7, C22-H, C24-H), 7.33 (td, 1H, J = 7.5, 1.4, C14-H), 7.28 (td, 1H, J = 7.5, 1.3, C15-H), 7.26 (t, 1H, J = 7.2, C23-H), 6.04 (br s, 1H, C1-NH_a), 5.58 (br s, 1H, C1-NH_b), 5.05 (dd, 1H, J = 7.1, 2.7, C6-H), 4.41 (d, 1H, J = 14.0, C10-H_a), 4.24 (d, 1H, J = 13.9, C10-H_b), 4.24 (d, 1H, J = 8.2, C9-H), 3.88 (s, 2H, C19-H_2), 3.79 (t, 1H, J = 7.6, C7-H), 3.49 (t, 1H, J = 3.3, C5-H), 3.28 (app dd, 1H, J = 6.2, 2.5, C4-H), 2.39 (d, 1H, J = 16.5, C3-H_a), 2.20 (dd, 1H, J = 16.7, 2.6, C3-H_b). FAB-MS (glycerol) *m/z* (rel int): 431 ([M+H]$^+$, 33). FAB-MS (NBA/NaI) *m/z* (rel int): 453 ([M+Na]$^+$, 40), 431 ([M+H]$^+$, 5). HRMS (NBA/NaI) *m/z* calcd for $C_{25}H_{22}N_2O_5Na$ 453.1426; found 453.1432.

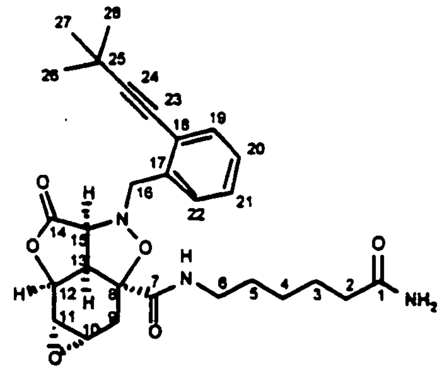


[2aS-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-Hexahydro-3-[[3-(3-methyl-3-buten-1-ynyl)phenyl]methyl]-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (*m*-(3-Methyl-3-buten-1-ynyl)benzyl tetracycle carboxamide, 40b). TLC: R_f

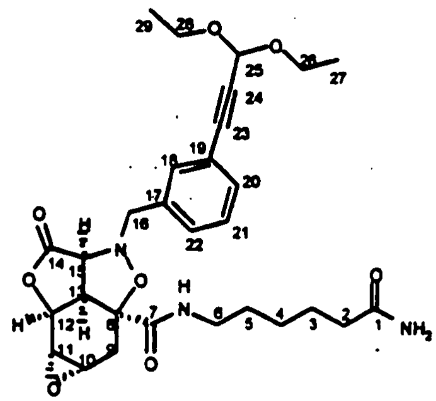
0.41 (4:1 CH_2Cl_2/THF); R_f 0.33 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.182 min, λ_{max} = (203), 212, 270, (282) nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.57 (s, 1H, C12-H), 7.37 (m, 2H, C14-H, C16-H), 7.33 (t, 1H, J = 7.4, C15-H), 6.09 (br s, 1H, C1-NH_a), 5.64 (br s, 1H, C1-NH_b), 5.38 (app q, 1H, J = 1.0, C20-H_Z), 5.36 (app q, 1H, J = 1.7, C20-H_E), 5.09 (dd, 1H, J = 7.2, 2.6, C6-H), 4.32 (d, 1H, J = 8.2, C9-H), 4.29 (d, 1H, J =13.9, C10-H_a), 4.00 (d, 1H, J =13.9, C10-H_b), 3.86 (t, 1H, J = 7.7, C7-H), 3.50 (t, 1H, J = 3.2, C5-H), 3.29 (dt, 1H, J = 3.7, 2.5, C4-H), 2.36 (dd, 1H, J =16.9, 1.6, C3-H_a), 2.26 (dd, 1H, J =16.8, 2.7, C3-H_b), 1.97 (dd, 3H, J = 2.5, 1.4, C21-H_3). FAB-MS (glycerol) m/z (rel int): 381 ([M+H]$^+$, 100). FAB-MS (NBA/NaI) m/z (rel int): 403 ([M+Na]$^+$, 27). HRMS (glycerol) m/z calcd for $C_{21}H_{21}N_2O_5$ 381.1450; found 381.1442.



[2a*S*-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-3-[[4-(4-Chlorophenyl)ethynyl]phenyl]methyl]hexahydro-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (*p*-(4-Chlorophenylethynyl)benzyl tetracycle carboxamide, 40c). TLC: R_f 0.40 (4:1 CH_2Cl_2/THF); R_f 0.30 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.618 min, λ_{max} = 202, (222), (276), 289, 303 nm. ^{1}H-NMR (400 MHz, CD_3CN): δ 7.51 (app d, 4H, J = 8.4, C13-H, C15-H, C20-H, C24-H), 7.41 (obs d, 2H, J = 8.7, C12-H, C16-H), 7.41 (obs d, 2H, J = 8.2, C21-H, C23-H), 6.06 (br s, 1H, C1-NH_a), 5.66 (br s, 1H, C1-NH_b), 5.10 (dd, 1H, J = 7.2, 2.7, C6-H), 4.35 (d, 1H, J = 8.2, C9-H), 4.32 (d, 1H, J = 14.2, C10-H_a), 4.03 (d, 1H, J = 14.2, C10-H_b), 3.87 (t, 1H, J = 7.7, C7-H), 3.50 (dd, 1H, J = 3.5, 2.9, C5-H), 3.29 (dt, 1H, J = 3.8, 2.5, C4-H), 2.35 (dd, 1H, J = 16.8, 1.5, C3-H_a), 2.25 (dd, 1H, J = 16.8, 2.8, C3-H_b). FAB-MS (glycerol) m/z (rel int): 451 ([M+H]$^+$, 46). HRMS (glycerol) m/z calcd for $C_{24}H_{20}ClN_2O_5$ 451.1061; found 451.1060.

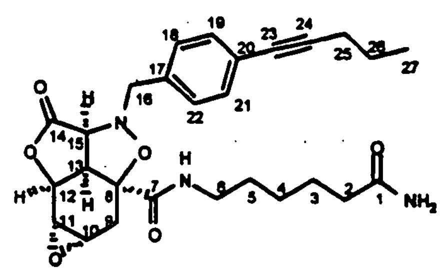


[2a*S*-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-*N*-(6-Amino-6-oxohexyl)-3-[[2-(3,3-dimethyl-1-butynyl)phenyl]methyl]hexahydro-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (*o*-(3,3-Dimethyl-1-butynyl)benzyl tetracycle ω-aminocaproic carboxamide, 40d). TLC: R_f 0.43 (9:1 CH_2Cl_2/MeOH); R_f 0.20 (1:1 CH_2Cl_2/THF). HPLC: t_R = 3.257 min, λ_{max} = 209, 247 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.44 (d, 1H, J = 7.5, C19-H), 7.35 (dd, 1H, J = 7.7, 1.2, C22-H), 7.32 (td, 1H, J = 7.7, 1.4, C20-H), 7.26 (td, 1H, J = 7.4, 1.3, C21-H), 6.14 (br s, 1H, C7-NH), 6.00 (br s, 1H, C1-NH_a), 5.50 (br s, 1H, C1-NH_b), 5.10 (dd, 1H, J = 7.2, 2.6, C12-H), 4.37 (d, 1H, J = 8.2, C15-H), 4.35 (d, 1H, J = 16.6, C16-H_a), 4.18 (d, 1H, J = 14.4, C16-H_b), 3.85 (t, 1H, J = 7.6, C13-H), 3.50 (t, 1H, J = 3.2, C11-H), 3.28 (dd, 1H, J = 6.0, 2.6, C10-H), 3.01 (m, 1H, C6-H_a), 2.88 (m, 1H, C6-H_b), 2.31 (d, 1H, J = 16.8, C9-H_a), 2.19 (dd, 1H, J = 16.7, 2.8, C9-H_b), 2.06 (t, 2H, J = 7.5, C2-H_2), 1.46 (m, 2H, C3-H_2), 1.31 (obs m, 2H, C5-H_2), 1.30 (s, 9H, C26-H_3, C27-H_3, C28-H_3), 1.13 (m, 2H, C4-H_2). FAB-MS (glycerol) m/z (rel int): 510 ($[M+H]^+$, 100). HRMS (glycerol) m/z calcd for $C_{28}H_{36}N_3O_6$ 510.2604; found 510.2612.



[2a*S*-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-*N*-(6-Amino-6-oxohexyl)-3-[[3-(3,3-diethoxy-1-propynyl)phenyl]methyl]hexahydro-2-oxo-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide(*m*-(3,3-Diethoxy-1-propynyl)benzyl tetracycle ω-aminocaproic carb xamide, 40e). TLC: R_f 0.39 (9:1 CH_2Cl_2/MeOH); R_f 0.17 (1:1 CH_2Cl_2/THF). HPLC: t_R

= 3.105 min, λ_{max} = 206, 243, 246 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.51 (s, 1H, C18-H), 7.43-7.34 (m, 3H, C20-H, C21-H, C22-H), 6.22 (br s, 1H, C7-NH), 6.00 (br s, 1H, C1-NH_a), 5.46 (br s, 1H, C1-NH_b), 5.45 (s, 1H, C25-H), 5.09 (dd, 1H, J = 7.3, 2.5, C12-H), 4.34 (d, 1H, J = 8.1, C15-H), 4.28 (d, 1H, J = 14.1, C16-H_a), 3.98 (d, 1H, J = 14.2, C16-H_b), 3.85 (t, 1H, J = 7.7, C13-H), 3.74 (m, 2H, C26-H_a, C28-H_a), 3.60 (m, 2H, C26-H_b, C28-H_b), 3.50 (app t, 1H, J = 3.5, 2.8, C11-H), 3.28 (app q, 1H, J = 5.8, 2.7, C10-H), 3.06 (m, 1H, J = 13.2, 6.4, C6-H_a), 2.94 (m, 1H, J = 13.2, 5.6, C6-H_b), 2.28 (dd, 1H, J = 16.9, 1.4, C9-H_a), 2.21 (dd, 1H, J = 16.8, 2.8, C9-H_b), 2.09 (t, 2H, J = 7.4, C2-H_2), 1.49 (quint, 2H, J = 7.5, C3-H_2), 1.24 (obs m, 2H, C5-H_2), 1.20 (t, 6H, J = 7.1, C27-H_3, C29-H_3), 1.16 (obs m, 2H, C4-H_2). FAB-MS (glycerol) m/z (rel int): 510 ([M-OEt]$^+$, 100), 556 ([M+H]$^+$, 7). FAB-MS (NBA/NaI) m/z (rel int): 578 ([M+Na]$^+$, 100), 510 ([M-OEt]$^+$, 11). HRMS (NBA/NaI) m/z calcd for $C_{29}H_{37}N_3O_8Na$ 578.2478; found 578.2475.

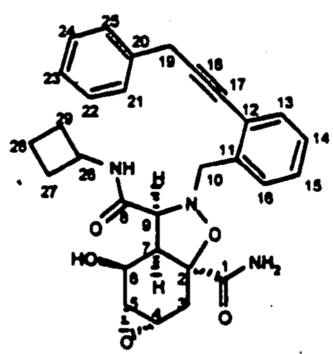


[2a*S*-(2aα, 4aα, 5aβ, 6aβ, 6bα, 6cα)]-*N*-(6-Amino-6-oxohexyl)hexahydro-2-oxo-3-[[4-(1-pentynyl)phenyl]methyl]-2*H*-furo[4,3,2-*cd*]oxireno[*f*][1,2]benzisoxazole-4a(3*H*)-carboxamide (*p*-(1-Pentynyl)benzyl tetracycle ω-aminocaproic carboxamide, 40f). TLC: R_f 0.31 (9:1 CH_2Cl_2/MeOH); R_f 0.18 (1:1 CH_2Cl_2/THF). HPLC: t_R = 3.255 min, λ_{max} = 203, 248, 251 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.35 (d, 2H, J = 8.3, C19-H, C21-H), 7.30 (d, 2H, J = 8.1, C18-H, C22-H), 6.21 (br s, 1H, C7-NH), 6.01 (br s, 1H, C1-NH_a), 5.50 (br s, 1H, C1-NH_b), 5.08 (dd, 1H, J= 7.2, 2.6, C12-H), 4.32 (d, 1H, J = 8.1, C15-H), 4.26 (d, 1H, J = 14.1, C16-H_a), 3.98 (d, 1H, J = 14.1, C16-H_b), 3.83 (t, 1H, J = 7.7, C13-H), 3.49 (app t, 1H, J = 3.2, C11-H), 3.28 (app dd, 1H, J = 5.9, 2.7, C10-H), 3.02 (m, 1H, C6-H_a), 2.91 (m, 1H, C6-H_b), 2.37 (t, 2H, J = 7.0, C25-H_2), 2.27 (br d, 1H, J = 16.8, C9-H_a), 2.20 (dd, 1H, J = 16.8, 2.9, C9-H_b), 2.08 (t, 2H, J = 7.7, C2-H_2), 1.59 (sxt, 2H, J= 7.2, C26-H_2), 1.49 (quint, 2H, J = 7.4, C3-H_2), 1.22 (m, 2H, C5-H_2), 1.17 (m, 2H, C4-H_2), 1.02 (t, 3H, J = 7.3, C27-H_3). FAB-MS (glycerol) m/z (rel int): 496 ([M+H]$^+$, 100). FAB-MS (NBA/NaI) m/z (rel int): 518 ([M+Na]$^+$, 100), 496 ([M+H]$^+$, 13). HRMS (glycerol) m/z calcd for $C_{27}H_{34}N_3O_6$ 496.2448; found 496.2463.

General Procedure for Lactone Aminolysis. To 50 mg (10.5 μmol) of the appropriate alkynylbenzyl tetracycle resin, **40R**, in a 2 mL Bio-Spin® column was added 2-hydroxypyridine (5.0 mg, 52.5 μmol, 5 equiv). THF (500 μL) was added and the tube was flushed briefly with Ar, capped, and shaken until the 2-hydroxypyridine was dissolved. The appropriate amine (25 equiv) was added and the tube was immediately capped, shaken, wrapped with parafilm, and wrapped in foil. After mixing 12-16 h at rt, the resin was washed (Method A) and dried under vacuum. Photolysis of the resin, **41R**, yielded the crude alkynylbenzyl γ-hydroxyamido tricycle, **41**, as a yellow oil.

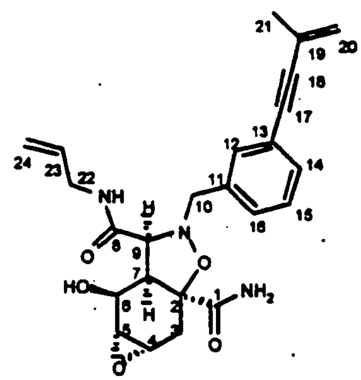
General Procedure for Lactone Aminolysis with α-Branched Amines. The same procedure was used as above except 10 equiv 2-hydroxypyridine and 50 equiv amine were used.

General Procedure for Lactone Aminolysis with Amine Hydrochlorides. To 50 mg (10.5 μmol) of the appropriate alkynylbenzyl tetracycle resin, **40R**, in a 2 mL Bio-Spin® column was added 2-hydroxypyridine (5.0 mg, 52.5 μmol, 5 equiv) and the amine hydrochloride (25 equiv). CH_2Cl_2 (300 μL) and DMF (200 μL) were added and the tube was flushed briefly with N_2. DIPEA (91.5 μL, 525 μmol, 50 equiv) was added and the tube was immediately capped, shaken, wrapped with parafilm, and wrapped in foil. After mixing 12-16 h at rt, the resin was washed (Method A + 3 × 20% DIPEA/CH_2Cl_2) and dried under vacuum. Photolysis of the resin, **41R**, yielded the crude alkynylbenzyl γ-hydroxyamido tricycle, **41**, as a yellow oil.

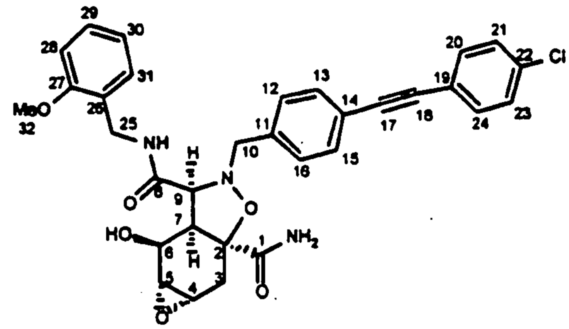


[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-(N^3-cyclobutyl)hexahydro-4-hydroxy-2-[[2-(3-phenyl-1-propynyl)phenyl]methyl]-oxireno[*f*]-1,2-benzisoxazole-3,6a(2*H*)-dicarboxamide (*o*-(3-Phenyl-1-propynyl)benzyl cyclobutylamido hydroxy tricycle carboxamide, 41a). TLC: R_f 0.14 (4:1 CH_2Cl_2/THF); R_f 0.06 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.141 min, λ_{max} = (203), 209, 247 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.56 (br s, 1H, C9-NH), 7.50 (dd, 1H, J = 7.3, 1.4, C13-H), 7.48 (obs d, 2H, C21-H, C25-H), 7.43 (dd, 1H, J = 7.5, 1.3, C16-H), 7.38 (t, 2H, J = 7.7, C22-H, C24-H), 7.32 (td, 1H, J = 7.5, 1.5, C14-H), 7.27 (td, 3H, J = 7.5, 1.4, C15-H, C23-H), 6.54 (br s, 1H, C1-NH_a), 5.89 (br s, 1H, C1-NH_b), 5.11 (d, 1H, J = 9.7, C6-OH), 4.43 (d, 1H, J = 12.8, C10-H_a), 4.11 (obs sxt, 1H, J = 8.1, C26-H), 4.11 (d, 1H, J = 12.8, C10-H_b),

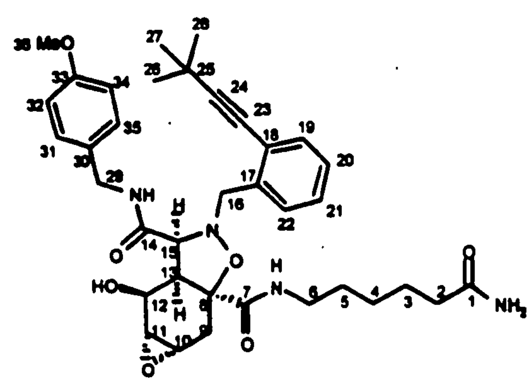
3.91 (s, 2H, C19-H_2), 3.90 (obs m, 1H, C6-H), 3.86 (d, 1H, J = 8.4, C9-H), 3.62 (app ddd, 1H, J = 8.4, 5.4, 1.4, C7-H), 3.12 (td, 1H, J = 4.0, 2.7, C4-H), 3.09 (dd, 1H, J = 4.0, 3.1, C5-H), 2.26 (dd, 1H, J = 16.4, 3.7, C3-H_a), 2.10 (obs m, 1H, C27-H_a), 2.05 (obs m, 1H, C29-H_a), 1.99 (dt, 1H, J = 16.4, 2.1, C3-H_b), 1.75 (app sxt, 2H, J = 10.2, C27-H_b, C29-H_b), 1.60 (m, 2H, C28-H_2). FAB-MS (glycerol) *m/z* (rel int): 502 ($[M+H]^+$, 62). FAB-MS (NBA/NaI) *m/z* (rel int): 524 ($[M+Na]^+$, 70), 502 ($[M+H]^+$, 13). HRMS (glycerol) *m/z* calcd for $C_{29}H_{32}N_3O_5$ 502.2342; found 502.2336.



[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-Hexahydro-4-hydroxy-2-[[3-(3-methyl-3-buten-1-ynyl)phenyl]methyl]-*N*³-(2-propenyl)oxireno[*f*]-1,2-benzisoxazole-3,6a(2*H*)-dicarboxamide (*m*-(3-Methyl-3-buten-1-ynyl)benzyl allylamido hydroxy tricycle carboxamide, 41b). TLC: R_f 0.12 (4:1 CH_2Cl_2/THF); R_f 0.07 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.034 min, λ_{max} = (203), 213, 270, (283) nm. ¹H-NMR (400 MHz, CD_3CN): δ 7.64 (br t, 1H, C8-NH), 7.51 (s, 1H, C12-H), 7.38 (dt, 1H, J = 7.0, 1.7, C14-H), 7.35 (dd, 1H, J = 5.7, 1.7, C16-H), 7.32 (t, 1H, J = 7.5, C15-H), 6.42 (s, 1H, C1-NH_a), 5.93 (s, 1H, C1-NH_b), 5.79 (ddt, 1H, J =17.2, 10.5, 5.3, C23-H), 5.37 (obs m, 1H, C20-H_Z), 5.36 (obs m, 1H, C20-H_E), 5.11 (dq, 1H, J =17.4, 1.6, C24-H_Z), 5.06 (dq, 1H, J =10.3, 1.5, C24-H_E), 5.02 (d, 1H, J = 9.4, C6-OH), 4.17 (d, 1H, J =13.7, C10-H_a), 3.93 (obs m, 1H, C6-H), 3.92 (obs d, 1H, J = 8.1, C9-H), 3.91 (obs d, 1H, J =13.9, C10-H_b), 3.78 (tt, 2H, J = 5.8, 1.4, C22-H_2), 3.64 (dd, 1H, J = 8.3, 5.1, C7-H), 3.14 (obs m, 1H, C5-H), 3.13 (obs m, 1H, C4-H), 2.26 (dd, 1H, J =16.3, 3.4, C3-H_a), 1.97 (t, 3H, J = 1.3, C21-H_3), 1.91 (obs dd, 1H, J = 1.9, C3-H_b). FAB-MS (glycerol) *m/z* (rel int): 438 ($[M+H]^+$, 60). FAB-MS (NBA/NaI) *m/z* (rel int): 438 ($[M+H]^+$, 78), 460 ($[M+Na]^+$, 43). HRMS (NBA/NaI) *m/z* calcd for $C_{24}H_{27}N_3O_5Na$ 460.1848; found 460.1853.

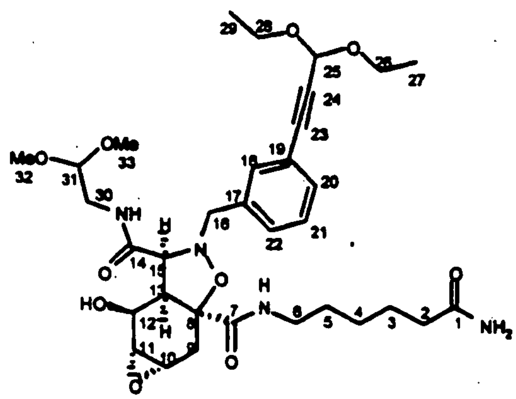


[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-2-[[4-[2-(4-Chlorophenyl)-1-ethynyl]phenyl]methyl]hexahydro-4-hydroxy-*N*3-[(2-methoxyphenyl)methyl]oxireno[*f*]-1,2-benzisoxazole-3,6a(2*H*)-dicarboxamide (*p*-(4-Chlorophenylethynyl)benzyl 2-methoxybenzylamido hydroxy tricycle carboxamide, 41c). TLC: R_f 0.13 (4:1 CH_2Cl_2/THF); R_f 0.06 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.778 min, λ_{max} = 201, 222, (276), 289, 303 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.97 (br t, 1H, C8-NH), 7.52 (d, 1H, J = 8.5, C20-H, C24-H), 7.49 (d, 1H, J = 8.1, C13-H, C15-H), 7.42 (obs d, 1H, J = 8.1, C21-H, C23-H), 7.42 (obs d, 1H, C12-H, C16-H), 7.27 (td, 1H, J = 7.9, 1.4, C29-H), 7.13 (dd, 1H, J = 7.3, C31-H), 6.97 (d, 1H, J = 8.1, C28-H), 6.89 (td, 1H, J = 7.4, C30-H), 6.37 (br s, 1H, C1-NH_a), 5.88 (br s, 1H, C1-NH_b), 5.13 (d, 1H, J = 10.0, C6-OH), 4.37 (dd, 1H, J =15.0, 6.2, C25-H_a), 4.33 (dd, 1H, J =14.8, 6.1, C25-H_b), 4.21 (d, 1H, J =13.8, C10-H_a), 3.95 (d, 1H, J = 8.6, C9-H), 3.93 (d, 1H, J =13.9, C10-H_b), 3.85 (s, 3H, C32-H), 3.83 (obs m, 1H, C6-H), 3.67 (dd, 1H, J = 8.4, 5.5, C7-H), 3.01 (t, 1H, J = 3.7, C5-H), 2.78 (m, 1H, C4-H), 2.15 (dd, 1H, J =16.4, 4.1, C3-H_a), 1.82 (dd, 1H, J =16.4, 2.6, C3-H_b). FAB-MS (glycerol) m/z (rel int): 588/590 ($[M+H]^+$, 52/28). FAB-MS (NBA/NaI) m/z (rel int): 610/612 ($[M+Na]^+$, 22/10). HRMS (glycerol) m/z calcd for $C_{32}H_{31}ClN_3O_6$ 588.1901; found 588.1896.



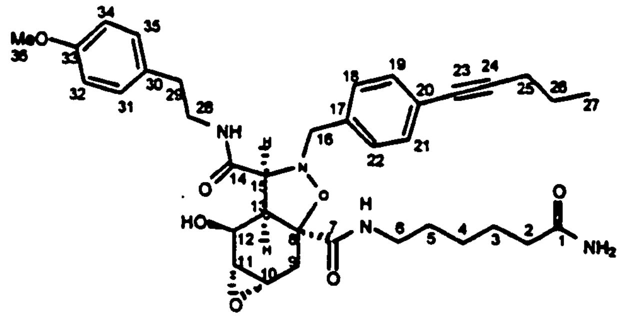
[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-*N*6a-(6-Amino-6-oxohexyl)-2-[[2-(3,3-dimethyl-1-butynyl)phenyl]methyl]hexahydro-4-hydr xy-*N*3-[(4-meth xyphenyl)methyl] xireno[*f*]-1,2-benzis xazole-3,6a(2*H*)-dicarboxamide (*o*-(3,3-Dimethyl-1-butynyl)benzyl 4-methoxybenzylamido hydroxy tricycle ω-aminocaproic carboxamide, 41d). TLC: R_f 0.43

(9:1 CH_2Cl_2/MeOH); R_f 0.20 (1:1 CH_2Cl_2/THF). HPLC: t_R = 3.385 min, λ_{max} = 202, 230, 245, (275) nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 8.09 (br t, 1H J = 5.8, C14-NH), 7.58 (d, 1H J = 7.5, C19-H), 7.33 (dd, 1H, J = 7.4, 1.1, C22-H), 7.31 (td, 1H, J = 7.3, 1.3, C20-H), 7.25 (td, 1H, J = 7.4, 1.3, C21-H), 7.11 (d, 2H, J = 8.7, C31-H, C35-H), 6.82 (d, 2H J = 8.6, C32-H, C34-H), 6.67 (br t, 1H, J = 5.7, C7-NH), 5.99 (br s, 1H, C1-NH_a), 5.46 (br s, 1H, C1-NH_b), 5.38 (d, 1H, J = 10.8, C12-OH), 4.26 (dd, 1H, J = 14.6, 6.5, C29-H_a), 4.25 (d, 1H, J = 13.1, C16-H_a), 4.18 (dd, 1H, J = 14.6, 6.1, C29-H_b), 4.08 (d, 1H, J = 13.1, C16-H_b), 3.97 (d, 1H, J= 8.8, C15-H), 3.84 (dd, 1H, J = 9.0, 5.3, C13-H), 3.74 (s, 3H, C36-H_3), 3.73 (obs m, 1H, C12-H), 3.11 (m, 2H, C6-H_2), 2.97 (dd, 1H, J = 4.2, 3.3, C11-H), 2.83 (td, 1H J = 5.4, 4.4, C10-H), 2.17 (obs m, 1H, C9-H_a), 2.06 (t, 2H, J = 7.4, C2-H_2), 1.62 (dd, 1h J = 16.4, 3.2, C9-H_b), 1.48 (m, 2H, C3-H_2), 1.38 (m, 2H, C5-H_2), 1.22 (m, 2H, C4-H_2), 1.30 (s, 9H, C26-H_3, C27-H_3, C28-H_3). FAB-MS (glycerol) m/z (rel int): 647 ([M+H]$^+$, 100). HRMS (glycerol) m/z calcd for $C_{36}H_{47}N_4O_7$ 647.3445; found 647.3463



[3S-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-N^{6a}-(6-Amino-6-oxohexyl)-2-[[3-(3,3-diethoxy-1-propynyl)phenyl]methyl]-N^3-(2,2-dimethoxyethyl)hexahydro-4-hydroxyoxireno[f]-1,2-benzisoxazole-3,6a(2H)-dicarboxamide (m-(3,3-Diethoxy-1-propynyl)benzyl 2,2-dimethoxyethylamido hydroxy tricycle ω-aminocaproic carboxamide, 41e). TLC: R_f 0.33 (9:1 CH_2Cl_2/MeOH); R_f 0.09 (1:1 CH_2Cl_2/THF). HPLC: t_R = 2.995 min, λ_{max} = 204, 243, 246 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.78 (br t, 1H, J = 5.5, C14-NH), 7.51 (s, 1H, C18-H), 7.40 (m, 2H, C20-H, C22-H), 7.35 (t, 1H, J = 7.5, C21-H), 6.68 (br t, 1H, J = 5.7, C7-NH), 6.07 (br s, 1H, C1-NH_a), 5.61 (br s, 1H, C1-NH_b), 5.46 (s, 1H, C25-H), 4.87 (d, 1H, J = 8.4, C12-OH), 4.38 (t, 1H, J = 5.0, C31-H), 4.12 (d, 1H, J = 13.9, C16-H_a), 4.01 (ddd, 1H, J = 8.4, 4.6, 3.7, C12-H), 3.89 (d, 1H, J = 13.9, C16-H_b), 3.86 (d, 1H, J = 8.0, C15-H), 3.74 (dq, 2H, J = 9.5, 7.1, C26-H_a, C28-H_a), 3.60 (dq, 2H, J = 9.4, 7.1, C26-H_b, C28-H_b), 3.53 (obs dd, 1H, J = 8.2, 4.9, C13-H), 3.37 (m, 1H, C30-H_a), 3.32 (s, 3H, C32-H_3), 3.32 (s, 3H, C33-H_3), 3.22 (obs m,

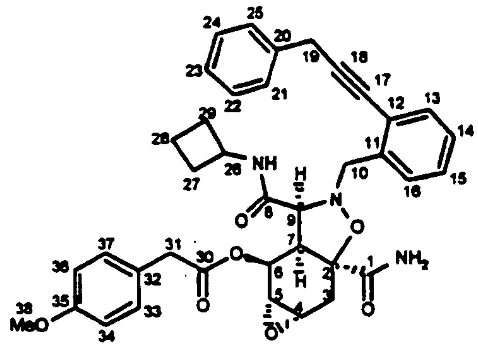
1H, C30-H_b), 3.19 (obs m, 3H, C6-H_2, C11-H), 3.14 (obs m, 1H, C10-H), 2.24 (dd, 1H, J = 16.3, 3.4, C9-H_a), 2.12 (obs t, 2H, J = 7.3, C2-H_2), 1.93 (obs m, 1H, C9-H_b), 1.53 (m, 2H, C3-H_2), 1.45 (m, 2H, C5-H_2), 1.27 (m, 2H, C4-H_2), 1.20 (t, 6H, J = 7.1, C27-H_3, C29-H_3). FAB-MS (glycerol) m/z (rel int): 661 ($[M+H]^+$, 55), 615 ($[M-OEt]^+$, 18). HRMS (glycerol) m/z calcd for $C_{33}H_{49}N_4O_{10}$ 661.3449; found 661.3464.



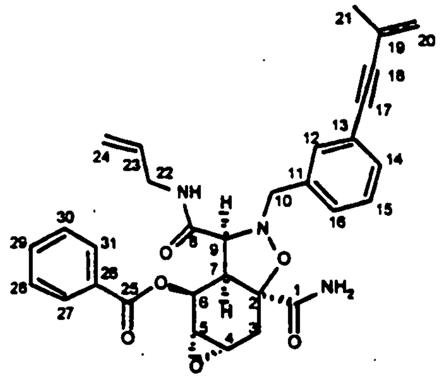
[3S-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-N^{6a}-(6-Amino-6-oxohexyl)hexahydro-4-hydroxy-N^3-[2-(4-methoxyphenyl)ethyl]-2-[[4-(1-pentynyl)phenyl]methyl]oxireno[f]-1,2-benzisoxazole-3,6a(2H)-dicarboxamide (p-(1-Pentynyl)benzyl 4-methoxyphenethylamido hydroxy tricycle ω-aminocaproic carboxamide, 41f). TLC: R_f 0.23 (9:1 CH_2Cl_2/MeOH); R_f 0.09 (1:1 CH_2Cl_2/THF). HPLC: t_R = 3.428 min, λ_{max} = 201, 232, 251, (279) nm. ^{1}H NMR (500 MHz, CD_3CN): δ 7.60 (br t, 1H, C14-NH), 7.32 (d, 2H, J = 8.1, C19-H, C21-H), 7.23 (d, 2H, J = 8.1, C18-H, C22-H), 7.11 (d, 2H, J = 8.6, C31-H, C35-H), 6.82 (d, 2H, J = 8.7, C32-H, C34-H), 6.63 (br t, 1H, J = 6.0, C7-NH), 6.05 (br s, 1H, C1-NH_a), 5.52 (br s, 1H, C1-NH_b), 5.05 (d, 1H, J = 8.8, C12-OH), 4.06 (d, 1H, J = 13.9, C16-H_b), 3.79 (m, 3H, C12-H, C15-H, C16-H_a), 3.73 (s, 3H, C36-H_3), 3.52 (obs m, 1H, C13-H), 3.42 (sxt, 1H, J = 6.3, C28-H_a), 3.36 (sxt, 1H, J = 6.2, C28-H_b), 3.12 (t, 2H, J = 6.6, C6-H_2), 3.02 (app dd, 1H, J = 7.0, 4.0, C10-H), 2.68 (td, 2H, J = 6.9, 2.7, C29-H_2), 2.37 (t, 2H, J = 7.0, C25-H_2), 2.16 (obs d, 1H, C9-H_a), 2.09 (t, 2H, J = 7.4, C2-H_2), 1.82 (dd, 1H, J = 16.2, 2.9, C9-H_b), 1.59 (sxt, 2H, J = 7.3, C26-H_2), 1.51 (m, 2H, C5-H_2), 1.41 (m, 2H, C3-H_2), 1.25 (m, 2H, C4-H_2), 1.02 (t, 3H, J = 7.4, C27-H_3). FAB-MS (glycerol) m/z (rel int): 647 ($[M+H]^+$, 85). FAB-MS (NBA/NaI) m/z (rel int): 669 ($[M+Na]^+$, 100), 647 ($[M+H]^+$, 60). HRMS (NBA/NaI) m/z calcd for $C_{24}H_{27}N_3O_5Na$ 669.3264; found 669.3252.

General Procedure for Alcohol Esterification. To 50 mg (10.5 μmol) of the appropriate alkynylbenzyl γ-hydroxyamido tricycle resin, 41R, in a 2 mL Bio-Spin column was added 200 μL CH_2Cl_2. The tube was flushed with Ar and cooled to 0 °C in an ice bath. The appropriate carboxylic acid (50 equiv) was dissolved or suspended in 400 μL CH_2Cl_2 in an oven-dried 2 mL Wheaton vial and activated with DIPC (41.1 μl, 262.5 μmol, 25 equiv). After

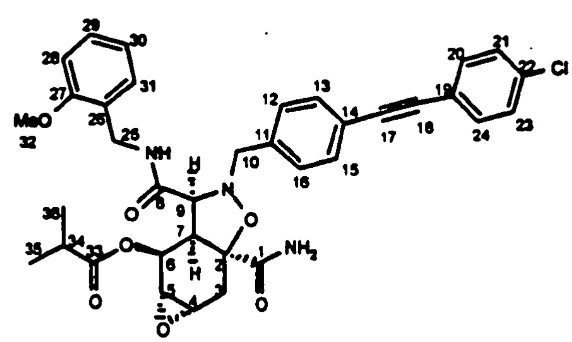
stirring at rt for 2 min, DIPEA (91.5 μL, 525 μL, 50 equiv) was added and stirring continued for another 3 min. The activated acid solution was then added to the resin via pipette with manual agitation followed by DMAP (6.4 mg, 52.5 μmol, 5 equiv) in 50 μL CH_2Cl_2. After standing 15 min at 0 °C, the tube was warmed to rt, wrapped with parafilm, wrapped in foil, and mixed at rt for 12-16 h. After washing (Method A + 3 × 20% DIPEA/CH_2Cl_2), photolysis of the resin, **42R**, yielded the crude alkynylbenzyl amido acyl tricycle, **42**, as a yellow oil.



[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-4-Methoxyphenylacetic acid, 6a-(aminocarbonyl)-2-[[2-(3-phenyl-1-propynyl)phenyl]methyl]octahydro-3-[(cyclobutylamino)carbonyl]oxireno[*f*]-1,2-benzisoxazol-4-yl ester (*o*-(3-Phenyl-1-propynyl)benzyl cyclobutylamido 4-methoxyphenylacetyl tricycle carboxamide, 42a). TLC: R_f 0.25 (4:1 CH_2Cl_2/THF); R_f 0.10 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.532 min, λ_{max} = 202, (209), 235, (250), (274) nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.49 (d, 3H, J = 7.4, C13-H, C21-H, C25-H), 7.46 (d, 1H, J = 7.7, C16-H), 7.36 (t, 2H, J = 7.7, C22-H, C24-H), 7.33 (td, 1H, J = 7.5, 1.6, C14-H), 7.29 (td, 1H, J = 7.6, 1.4, C15-H), 7.25 (t, 1H, J = 7.5, C23-H), 7.17 (d, 2H, J = 8.7, C33-H, C37-H), 6.87 (d, 1H, J = 8.7, C8-NH), 6.84 (d, 2H, J = 8.7, C34-H, C36-H), 6.64 (br s, 1H, C1-NH_a), 5.91 (br s, 1H, C1-NH_b), 5.31 (t, 1H, J = 3.9, C6-H), 4.61 (d, 1H, J = 12.3, C10-H_a), 4.17 (d, 1H, J = 12.3, C10-H_b), 3.92 (app d, 2H, J = 2.7, C19-H_2), 3.81 (d, 1H, J = 8.6, C9-H), 3.80 (obs m, 1H, C26-H), 3.75 (s, 3H, C38-H_3), 3.69 (dd, 1H J = 8.5, 3.8, C7-H), 3.48 (d, 1H, J = 15.5, C31-H_a), 3.37 (d, 1H, J = 15.5, C31-H_b), 3.31 (t, 1H, J = 4.1, C5-H), 3.10 (ddd, 1H, J = 4.2, 3.0, 1.9, C4-H), 2.40 (dd, 1H, J = 16.2, 3.0, C3-H_a), 2.34 (dd, 1H, J = 16.1, 1.8, C3-H_b), 1.94 (obs m, 1H, C27-H_a), 1.84 (obs m, 1H, C29-H_a), 1.63 (quint, 1H, J = 9.8, C27-H_b), 1.50 (m, 2H, C28-H_2), 1.33 (quint, 1H, J = 9.9, C29-H_b). FAB-MS (glycerol) *m/z* (rel int): 650 ([M+H]$^+$, 65). FAB-MS (NBA/NaI) *m/z* (rel int): 672 ([M+Na]$^+$, 35), 524 ([M+H]$^+$, 9). HRMS (glycerol) *m/z* calcd for $C_{38}H_{40}N_3O_7$ 650.2866; found 650.2836.

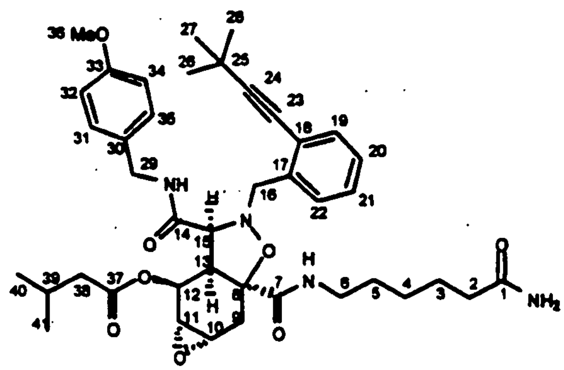


[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-Benzoic acid, 6a-(aminocarbonyl)-2-[[3-(3-methylbut-3-en-1-ynyl)phenyl]methyl]octahydro-3-[[(2-propenyl)amino]carbonyl]oxireno[*f*]-1,2-benzisoxazol-4-yl ester (*m*-(3-Methyl-3-buten-1-ynyl)benzyl allylamido benzoyl tricycle carboxamide, 42b). TLC: R_f 0.22 (4:1 CH_2Cl_2/THF); R_f 0.13 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 3.601 min, λ_{max} = 201, 220, (236), 270, (282) nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 8.15 (dd, 2H, *J* = 8.2, 1.2, C27-H, C31-H), 7.64 (tt, 1H, *J* = 7.4, 1.5, C29-H), 7.56 (s, 1H, C12-H), 7.55 (obs t, 2H, *J* = 7.6, C28-H, C30-H), 7.37 (m, 3H, C14-H, C15-H, C16-H), 6.71 (br t, 1H, C8-NH), 6.53 (br s, 1H, C1-NH_a), 5.99 (br s, 1H, C1-NH_b), 5.63 (t, 1H, *J* = 3.9, C6-H), 5.40 (m, 2H, C20-H_2), 5.22 (ddt, 1H, *J* = 16.8, 10.3, 6.1, C23-H), 4.70 (app dq, 1H, *J* = 10.2, 1.3, C24-H_E), 4.64 (app dq, 1H, *J* = 17.1, 1.5, C24-H_Z), 4.26 (d, 1H, *J* = 14.1, C10-H_a), 3.96 (d, 1H, *J* = 14.1, C10-H_b), 3.86 (d, 1H, *J* = 8.0, C9-H), 3.77 (dd, 1H, *J* = 8.0, 3.6, C7-H), 3.54 (obs m, 1H, C5-H), 3.53 (obs m, 1H, C22-H_a), 3.17 (app quint, 1H, *J* = 2.1, C4-H), 3.01 (dddt, 1H, *J* = 15.2, 6.2, 4.9, C22-H_b), 2.44 (dd, 1H, *J* = 16.6, 2.5, C3-H_a), 2.40 (dd, 1H, *J* = 16.5, 1.8, C3-H_b), 1.99 (app t, 3H, *J* = 1.2, C21-H_3). FAB-MS (glycerol) *m/z* (rel int): 542 ([M+H]$^+$, 100). FAB-MS (NBA/NaI) *m/z* (rel int): 564 ([M+Na]$^+$, 100), 542 ([M+H]$^+$, 18). HRMS (NBA/NaI) *m/z* calcd for $C_{31}H_{31}N_3O_6Na$ 564.2111; found 564.2100.



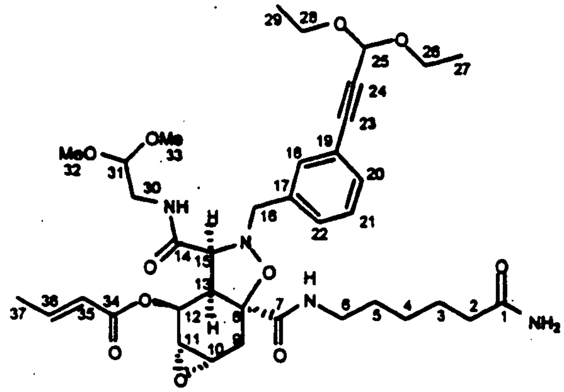
[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-2-Methylpropanoic acid, 6a-(aminocarbonyl)-2-[[4-[2-(4-chlorophenyl)-1-ethynyl]phenyl]methyl]-3-[[[(2-methoxyphenyl)methyl]amino]carbonyl]octahydrooxireno[*f*]-1,2-benzisoxazol-4-yl ester (*p*-(4-Chlorophenylethynyl)benzyl 2-methoxybenzylamido is butyryl tricycle carb xamide,

42c). TLC: R_f 0.19 (4:1 CH_2Cl_2/THF); R_f 0.12 (1:1 CH_2Cl_2/EtOAc). HPLC: t_R = 4.072 min, λ_{max} = 202, 222, (270), 291, 304 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.52 (d, 2H, J = 8.5, C20-H, C24-H), 7.45 (d, 2H, J = 8.1, C13-H, C15-H), 7.42 (d, 2H, J = 8.5, C21-H, C23-H), 7.39 (obs m, 1H, C8-NH), 7.35 (d, 2H, J = 8.1, C12-H, C16-H), 7.25 (td, 1H, J = 7.8, 1.7, C29-H), 7.02 (dd, 1H, J = 7.4, 1.3, C31-H), 6.94 (d, 1H, J = 8.2, C28-H), 6.87 (t, 1H, J = 7.5, C30-H), 6.48 (br s, 1H, C1-NH_a), 5.92 (br s, 1H, C1-NH_b), 5.36 (t, 1H, J = 4.0, C6-H), 4.39 (dd, 1H, J =14.6, 7.3, C25-H_a), 4.18 (d, 1H, J =14.1, C10-H_a), 4.06 (dd, 1H, J =14.7, 4.8, C25-H_b), 3.87 (d, 1H, J =14.2, C10-H_b), 3.78 (obs d, 1H, J = 8.6, C9-H), 3.76 (s, 3H, C32-H_3), 3.67 (dd, 1H, J = 8.4, 3.9, C7-H), 3.37 (t, 1H, J = 4.2, C5-H), 3.15 (dt, 1H, J = 4.1, 2.6, C4-H), 2.40 (sept, 1H, J = 7.0, C34-H), 2.35 (dd, 1H, J = 16.4, 2.9, C3-H_a), 2.29 (dd, 1H, J = 16.2, 2.0, C3-H_b), 1.13 (d, 3H, J = 7.1, C35-H_3), 1.09 (d, 3H, J = 7.0, C36-H_3). FAB-MS (glycerol) m/z (rel int): 658/660 ($[M+H]^+$, 6/3). FAB-MS (NBA/NaI) m/z (rel int): 680/682 ($[M+Na]^+$, 20/10), 658/660 ($[M+H]^+$, 12/6). HRMS (NBA/NaI) m/z calcd for $C_{36}H_{36}ClN_3O_7Na$ 680.2139; found 680.2147.

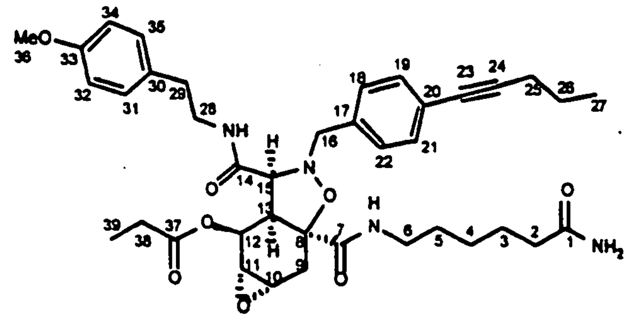


[3S-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-3-Methylbutanoic acid, 6a-[[(6-amino-6-oxohexyl)amino]carbonyl]-2-[[2-(3,3-dimethyl-1-butynyl)phenyl]methyl]-3-[[[(4-methoxyphenyl)methyl]amino]carbonyl]octahydrooxireno[*f*]-1,2-benzisoxazol-4-yl ester (*o*-(3,3-Dimethyl-1-butynyl)benzyl 4-methoxybenzylamido isovaleryl tricycle ω-aminocaproic carboxamide, 42d). TLC: R_f 0.49 (9:1 CH_2Cl_2/MeOH); R_f 0.29 (1:1 CH_2Cl_2/THF). HPLC: t_R = 3.742 min, λ_{max} = (203), (215), 232, 247, (275) nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.46 (d, 1H, J = 8.0, C19-H), 7.27 (obs dd, 1H, J = 7.6, 1.2, C22-H), 7.25 (obs td, 1H, J = 7.5, 1.6, C20-H), 7.20 (td, 1H, J = 7.4, 1.2, C21-H), 7.18 (obs br t, 1H, C14-NH), 6.88 (d, 2H, J = 8.5, C31-H, C35-H), 6.83 (br t, 1H, C7-NH), 6.77 (d, 2H, J = 8.7, C32-H, C34-H), 5.97 (br s, 1H, C1-NH_a), 5.45 (br s, 1H, C1-NH_b), 5.31 (t, 1H, J = 4.1, C12-H), 4.38 (d, 1H, J = 13.1, C16-H_a), 4.05 (d, 1H, J = 13.2, C16-H_b), 3.99 (dd, 1H, J = 14.6, 6.3, C29-H_a), 3.91 (dd, 1H, J = 14.6, 5.9, C29-H_b), 3.87 (d, 1H, J = 8.9, C15-H), 3.77 (dd, 1H, J = 8.8, 4.1, C13-H), 3.74 (s, 3H, C36-H_3), 3.40 (t, 1H, J = 4.2, C11-H), 3.18 (q, 2H, J = 6.7, C6-H_2), 3.15 (obs m, 1H, C10-H), 2.29 (app s, 2H,

C9-H_2), 2.09 (obs m, 5H, C2-H_2, C38-H_2, C39-H), 1.52 (obs m, 2H, C3-H_2), 1.47 (obs m, 2H, C5-H_2), 1.31 (s, 9H, C26-H_3, C27-H_3, C28-H_3), 1.27 (obs m, 2H, C4-H_2), 0.89 (t, 6H, J = 5.9, C40-H_3, C41-H_3). FAB-MS (glycerol) m/z (rel int): 731 ($[M+H]^+$, 13). FAB-MS (NBA/NaI) m/z (rel int): 753 ($[M+Na]^+$, 100), 731 ($[M+H]^+$, 22). HRMS (NBA/NaI) m/z calcd for $C_{41}H_{54}N_4O_8Na$ 753.3839; found 753.3842.



[3*S*-(3α, 3aβ, 4α(*E*), 4aα, 5aα, 6aβ)]-2-Butenoic acid, 6a-[[(6-amino-6-oxohexyl)amino]carbonyl]-2-[[3-(3,3-diethoxy-1-propynyl)phenyl]methyl]-3-[[(2,2-dimethoxyethyl)amino]carbonyl]octahydrooxireno[*f*]-1,2-benzisoxazol-4-yl ester (*m*-(3,3-Diethoxy-1-propynyl)benzyl 2,2-dimethoxyethylamido crotonyl tricycle ω-aminocaproic carboxamide, 42e). TLC: R_f 0.40 (9:1 CH_2Cl_2/MeOH); R_f 0.16 (1:1 CH_2Cl_2/THF). HPLC: t_R = 3.285 min, λ_{max} = 207, 241, 246 nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.53 (s, 1H, C18-H), 7.40 (m, 3H, C20-H, C21-H, C22-H), 7.09 (obs br t, 1H, C14-NH), 7.05 (dq, 1H, J = 15.4, 6.9, C36-H), 6.78 (br t, 1H, J = 6.5, C7-NH), 6.04 (s, 1H, C1-NH_a), 5.83 (dq, 1H, J = 15.4, 1.7, C35-H), 5.55 (s, 1H, C1-NH_b), 5.46 (s, 1H, C25-H), 5.34 (t, 1H, J = 4.0, C12-H), 4.25 (dd, 1H, J = 5.8, 4.5, C31-H), 4.04 (d, 1H, J = 14.3, C16-H_a), 3.89 (d, 1H, J = 14.3, C16-H_b), 3.74 (obs m, 2H, C26-H_a, C28-H_a), 3.73 (obs m, 1H, C15-H), 3.64 (dd, 1H, J = 8.0, 4.0, C13-H), 3.60 (app dq, 2H, J = 9.5, 7.1, C26-H_b, C28-H_b), 3.43 (dd, 1H, J = 7.8, 4.5, C30-H_a), 3.40 (obs m, 1H, C11-H), 3.29 (s, 3H, C32-H_3), 3.27 (s, 3H, C33-H_3), 3.24 (m, 2H, C6-H_2), 3.15 (m, 1H, C10-H), 2.86 (ddd, 1H, J =13.7, 5.8, 3.8, C30-H_b), 2.27 (app d, 2H, J = 2.4, C9-H_2), 2.12 (m, 2H, C2-H_2), 1.89 (dd, 3H, J = 6.9, 1.7, C37-H_3), 1.57 (m, 2H, C3-H_2), 1.53 (m, 2H, C5-H_2), 1.31 (m, 2H, C4-H_2), 1.20 (t, 6H, J= 7.1, C27-H_3, C29-H_3). FAB-MS (glycerol) m/z (rel int): 729 ($[M+H]^+$, 13). FAB-MS (NBA/NaI) m/z (rel int): 751 ($[M+Na]^+$, 100), 729 ($[M+H]^+$, 6). HRMS (NBA/NaI) m/z calcd for $C_{37}H_{52}N_4O_{11}Na$ 751.3530; found 751.3536.



[3*S*-(3α, 3aβ, 4α, 4aα, 5aα, 6aβ)]-Propanoic acid, 6a-[[(6-amino-6-oxohexyl)amino]carbonyl]-3-[[[2-(4-methoxyphenyl)ethyl]amino]carbonyl]octahydro-2-[[4-(1-pentynyl)phenyl]methyl]oxireno[*f*]-1,2-benzisoxazol-4-yl ester (*p*-(1-Pentynyl)benzyl 4-methoxyphenethylamido propionyl tricycle ω-aminocaproic carboxamide, 42f). TLC: R_f 0.33 (9:1 CH_2Cl_2/MeOH); R_f 0.23 (1:1 CH_2Cl_2/THF). HPLC: t_R = 3.602 min, λ_{max} = 202, 231, 252, (280) nm. ^{1}H-NMR (500 MHz, CD_3CN): δ 7.33 (d, 2H, *J* = 8.1, C19-H, C21-H), 7.20 (d, 2H, *J* = 8.1, C18-H, C22-H), 7.04 (d, 2H, *J* = 8.4, C31-H, C35-H), 6.90 (br t, 1H, *J* = 5.5, C14-NH), 6.74 (d, 2H, *J* = 8.7, C32-H, C34-H), 6.72 (br t, 1H, *J* = 5.5, C7-NH), 6.03 (br s, 1H, C1-NH_a), 5.55 (br s, 1H, C1-NH_b), 5.25 (t, 1H, *J* = 4.0, C12-H), 3.98 (d, 1H, *J* = 14.2, C16-H_a), 3.74 (d, 1H, *J* = 14.4, C16-H_b), 3.67 (s, 3H, C36-H_3), 3.63 (d, 1H, *J* = 8.4, C15-H), 3.60 (dd, 1H, *J* = 8.4, 4.1, C13-H), 3.50 (obs m, 1H, C28-H_a), 3.32 (app t, 1H, *J* = 4.2, C11-H), 3.20 (obs m, 1H, C6-H_a), 3.16 (obs m, 1H, C6-H_b), 3.14 (obs m, 1H, C10-H), 3.02 (m, 1H, C28-H_b), 2.64-2.50 (m, 2H, C29-H_2), 2.38 (t, 2H, *J* = 7.0, C25-H_2), 2.28-2.16 (m, 4H, C9-H_2, C38-H_2), 2.10 (t, 2H, *J* = 7.3, C2-H_2), 1.59 (sxt, 2H, *J* = 7.2, C26-H_2), 1.53 (quint, 2H, *J* = 7.7, C3-H_2), 1.47 (m, 2H, C5-H_2), 1.27 (m, 2H, C4-H_2), 1.03 (t, 3H, *J* = 7.5, C39-H_3), 1.02 (t, 3H, *J* = 7.3, C27-H_3). FAB-MS (glycerol) *m/z* (rel int): 703 ($[M+H]^+$, 18). FAB-MS (NBA/NaI) *m/z* (rel int): 725 ($[M+Na]^+$, 100), 703 ($[M+H]^+$, 17). HRMS (NBA/NaI) *m/z* calcd for $C_{39}H_{50}N_4O_8Na$ 725.3526; found 725.3527.

IV. Building Block Testing:

Building Block Testing – General. All solids were measured to within 10%. All liquids were dispensed via Gilson automatic pipettemen with polypropylene tips. Reactions were performed using the small-scale solid phase reaction procedures described above. Resin samples were photolyzed in sets of 11 for 1 h. After photolysis, the samples were centrifuged briefly and 10 μL of the supernatant was submitted for HPLC analysis. An additional 5 μL was diluted to 50 μL with CH_3CN and submitted for LC-MS analysis (10 μL injection). Where necessary, additional samples were removed for TLC and FAB-MS analysis.

To ensure that all of the building blocks included in the library synthesis were viable coupling partners, a total of 235 building blocks were tested in the Sonogashira/Castro-Stephens, lactone aminolyis, and esterification reactions (Figures 65-67). A representative sample of the LC-MS data is shown in Figure 56 of the Manuscript. Complete HPLC (52 pages) and LCMS data (235 pages) have also been obtained. These data are summarized in tabular format below (Tables A-C).

Building Block Testing – Alkynes. 2-Iodobenzyl tetracycle ω-aminocaproic-Anp-TentaGel resin **39dR** (10 mg, 0.24 meq/g, 2.39 μmol, 1.0 equiv), copper(I) iodide (1.0 mg, 5.26 μmol, 2.2 equiv), and bis(triphenylphosphine)palladium(II) chloride (1.84 mg, 2.63 μmol, 1.1 equiv) or tetrakis(triphenylphosphine)palladium(0) for polyynes (3.04 mg, 2.63 μmol, 1.1 equiv) were combined and 100 μL DMF was added, followed by DIPEA (12.5 μL, 71.76 μmol, 30 equiv for monoynes; 29.17 μL, 167.43 μmol, 70 equiv for diynes; or 43.75 μL, 251.1 μmol, 105 equiv for triynes). The tube was vortexed vigorously, centrifuged briefly, then the appropriate alkyne (47.84 μmol, 20 equiv for monoynes; 119.6 μmol, 50 equiv for diynes; or 179.4 μmol, 75 equiv for triynes) was added as a neat liquid or solid. The tube was again vortexed vigorously, centrifuged briefly, wrapped with parafilm, and finally vortexed gently for 1 h. After washing, the resin was photolyzed in 125 μL CH_3CN.

Building Block Testing – Amines. *o*-(3,3-Dimethyl-1-butynyl)benzyl tetracycle ω-aminocaproic-Anp-TentaGel resin **40dR** (5 mg, 0.24 meq/g, 1.21 μmol, 1.0 equiv) and solid amines where appropriate (30.23 μmol, 25 equiv for non-α-branched amines; 60.49 μmol, 50 equiv for α-branched amines) were combined, then 2-hydroxypyridine (0.575 mg, 6.05 μmol, 5 equiv for non-α-branched amines; 1.150 mg, 12.09 μmol, 10 equiv for α-branched amines) was added as a 50 μL stock solution in THF (free amines) or 2:1 CH_2Cl_2/DMF (amine hydrochlorides). Neat liquid amines (30.23 μmol, 25 equiv for non-α-branched amines; 60.49 μmol, 50 equiv for α-branched amines) were added where appropriate. DIPEA was added as necessary to neutralize amine hydrochlorides (10.53 μL, 60.46 μmol, 50 equiv for non-α-branched monohydrochlorides; 21.06 μL, 120.92 μmol, 100 equiv for non-α-branched dihydrochlorides and α-branched monohydrochlorides; 42.12 μL, 241.84 μmol, 200 equiv for α-branched dihydrochlorides). The tubes were wrapped with teflon tape and parafilm and vortexed gently for 13 h. After washing, the resin was photolyzed in 60 μL CH_3CN.

Building Block Testing – Acids. In 2 mL oven-dried Wheaton vials fitted with teflon septum caps and stir bars were placed the appropriate carboxylic acids (292.6 μmol, 250 equiv) and 182.62 μL CH_2Cl_2. DIPC (22.90 μL, 146.3 μmol, 125 equiv) was added to each vial and the

mixtures stirred for 2 min. DIPEA (50.95 μL, 292.6 μmol, 250 equiv; 101.9 μL, 585.2 μmol, 500 equiv for amino acid hydrochlorides) was added to each vial and the mixtures stirred for another 5 min. Approximately 1/5th of each preactivation mixture (60 μL normally; 70 μL for hydrochlorides; 25 equiv activated acid) was added to *o*-(3,3-dimethyl-1-butynyl)benzyl 4-methoxybenzylamido hydroxy tricycle ω-aminocaproic-Anp-TentaGel resin **41dR** (5 mg, 0.23 meq/g, 1.17 μmol, 1.0 equiv). DMAP (0.715 mg, 5.85 μmol, 5 equiv) was added to each tube as a 10 μL stock solution in CH_2Cl_2 and the tubes were wrapped with teflon tape and parafilm then vortexed gently for 14 h. The resin was exposed to the standard wash procedure with an additional 20% DIPEA in CH_2Cl_2 wash inserted between the CH_2Cl_2 and DMF wash steps. Finally, the resin was photolyzed in 60 μL CH_3CN.

V. Test Library Synthesis and Deconvolution:

Test Library Synthesis – General. All solids were measured to within 10%. All liquids were dispensed via Gilson automatic pipettemen with polypropylene tips. Reactions were performed in tared 2 mL BioSpin® columns. Resin was distributed to each column as 1 mL of an 8 mL isopicnic slurry in DMSO/CH_2Cl_2 with a P1000 pipetteman fitted with a P1000 polypropylene tip trimmed by approximately 2 mm. The resin was washed with distd THF and distd CH_2Cl_2, dried, and weighed. This method of resin distribution proved consistent to within ±5% (data not shown). After reaction according to the medium-scale solid phase procedures described above, the resin portions were washed using the standard wash procedure (Method A) and a sample was photolyzed for 2 h followed by HPLC and LC-MS analysis of the supernatant. The remaining resins were pooled in a PD-10 column via vacuum cannula transfer from the reaction vessels and mixed thoroughly by repeated washing with CH_2Cl_2.

A representative sample of the LC-MS data is shown in Figure 56. Complete HPLC (14 pages) and LC-MS data (168 pages) have been obtained. These data are summarized in tabular format below (Tables D-F).

Test Library Synthesis – 3-Alkynylbenzyl tetracycle-Anp-TentaGel resins (43R{X,1,1}). To each of seven aliquots of 3-iodobenzyl tetracycle-Anp-TentaGel resin **39bR** (31.25 mg, 0.25 meq/g, 7.68 μmol, 1.0 equiv) was added in sequence copper(I) iodide (3.2 mg, 16.90 μmol, 2.2 equiv), bis(triphenylphosphine)palladium(II) chloride (5.9 mg, 8.45 μmol, 1.1 equiv), and 300 μL DMF. The tubes were flushed with Ar and vortexed briefly. DIPEA (40.15 μL, 230.5 μmol, 30 equiv) was added to each tube followed by the appropriate alkyne (153.65 μmol, 20 equiv). The tubes were wrapped with parafilm and mixed for 2 h. After washing, approx 1 mg of resin was removed from each tube and photolyzed in 30 μL CH_3CN. 10 μL was

submitted for HPLC analysis and an additional 4 μL was diluted to 30 μL and submitted for LC-MS analysis (10 μL injection). The remaining resin was pooled to yield a mixture of eight 3-alkynylbenzyl tetracycle-Anp-TentaGel resins **43R{X,1,1}**.

Test Library Synthesis – 3-Alkynylbenzyl γ-hydr xyamido tricycle-Anp-TentaGel resins (43R{X,X,1}). To each of seven aliquots of 3-alkynylbenzyl tetracycle-Anp-TentaGel resin **43R{X,1,1}** (30 mg, 0.25 meq/g avg 7.43 μmol avg, 1.0 equiv) was added 2-hydroxypyridine (3.53 mg, 37.14 μmol, 5 equiv) as a 300 μL stock solution in THF. An additional 5 equiv of 2-hydroxypyridine was added as a solid to Pool #4 (α-branched amine). The tubes were flushed with Ar, and the appropriate amine (185.7 μmol, 25 equiv; 371.4 μmol, 50 equiv for Pool #4) was added to each. The tubes were wrapped with teflon tape and parafilm and mixed for 15 h. After washing, approx 2 mg of resin was removed from each tube and photolyzed in 40 μL CH_3CN. 10 μL was submitted for HPLC analysis and an additional 10 μL was submitted without dilution for LC-MS analysis. The remaining resin was pooled to yield a mixture of sixty-four 3-alkynylbenzyl γ-hydroxyamido tricycle-Anp-TentaGel resins **43R{X,X,1}**.

Test Library Synthesis – 3-Alkynylbenzyl amido acyl tricycle-Anp-TentaGel resins (43R{X,X,1} through 43R{X,X,8}). In each of seven 2 mL oven-dried Wheaton vials fitted with septum caps and stir bars were placed the appropriate carboxylic acids (326.5 μmol, 50 equiv) and 300 μL CH_2Cl_2. DIPC (25.60 μL, 163.25 μmol, 25 equiv) was added to each vial and the mixtures were stirred for 2 min. DIPEA (56.9 μL, 326.5 μmol, 50 equiv) was added to each vial and the mixtures were stirred for another 5 min. Seven aliquots of 3-alkynylbenzyl γ-hydroxyamido tricycle-Anp-TentaGel resin **43R{X,X,1}** (27 mg, 0.24 meq/g avg, 6.53 μmol avg, 1.0 equiv) were each swollen with 100 μL CH_2Cl_2, flushed with Ar, and cooled to 0°C in an ice bath. The appropriate preactivated acid was then added to each tube followed by DMAP (3.99 mg, 32.65 μmol, 5 equiv) as a 50 μL stock solution in CH_2Cl_2. Each tube was vortexed briefly and allowed to stand at 0°C for 15 min. The tubes were then warmed to rt, wrapped with teflon tape and parafilm and mixed for 10 h. A 20% DIPEA/CH_2Cl_2 wash was added between the CH_2Cl_2 and DMF steps of the standard wash procedure. After drying, 12 mg of each 3-alkynylbenzyl amido acyl tricycle-Anp-TentaGel resin **43R{X,X,1}** through **43R{X,X,8}** was photolyzed in 120 μL CH_3CN. The supernatant from each tube was filtered through a BioSpin® column into a new Eppendorf tube and the photolysis tubes and resin rinsed with an additional 50 μL CH_3CN. The eight samples were concentrated for 15 min on a Savant AES 1000 SpeedVac at Low Drying Rate, redissolved in 11 μL CH_3CN, and transferred to an HPLC

autosampler vial. Each tube was rinsed with an additional 11 μL CH_3CN transferred to the same vials. 10 μL of each sample was submitted for HPLC analysis and 10 μL was submitted for LC-MS analysis.

Test Library Deconvoluti n Syntheses. TGF-β-responsive reporter gene assay activity was detected in pool **43{X,X,8}**, which contains 64 compounds. To deconvolute this activity, the eight-compound subpools **43{X,1,8}** through **43{X,8,8}** were synthesized essentially as described above from 3-iodobenzyl tetracycle-Anp-TentaGel resin **39bR** (12.5 mg, 0.25 meq/g, 3.07 μmol, 1.0 equiv) except that the resin portions were not repooled after lactone aminolysis. All eight portions were acylated separately with **Acid 8** (monomethyl terephthalic acid). The presence of all eight expected compounds in each pool was verified by LC-MS analysis (data not shown).

Pool **43{X,X,3}** showed lower activity in the TGF-β-responsive reporter gene assay and was deconvoluted as a negative control. The eight-compound subpools **43{X,1,3}** through **43{X,8,3}** were synthesized as above and acylated with **Acid 3** (methoxyacetic acid).

Of the 16 eight-compound subpools, **43{X,8,3}** showed the highest activity in the TGF-β-responsive reporter gene assay. To deconvolute this activity, the eight individual compounds comprising the subpool, **43{1,8,3}** through **43{8,8,3}**, were synthesized in parallel essentially as described for Demonstration Compounds in the Manuscript from 3-iodobenzyl tetracycle-Anp-TentaGel resin **39bR** (150 mg, 0.25 meq/g, 36.88 μmol, 1.0 equiv). The final acylated products, as well as the 3-alkynylbenzyl tetracycle intermediates, **43{1,1,1}** through **43{8,1,1}**, and the γ-hydroxyamido tricycle intermediates, **43{1,8,1}** through **43{8,8,1}**, were analyzed by ^{1}H-NMR, TOF-ESI-MS, and HR-TOF-ESI-MS. All compounds exhibited satisfactory ^{1}H-NMR data and were recovered in approximately 80-90% purity.

43{1,1,1} HPLC: $t_R = 3.022$ min. TOF-ESI-MS *m/z* (rel int): 381 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{21}H_{21}N_2O_5$ 381.1450; found 381.1449.

43{2,1,1} HPLC: $t_R = 2.588$ min. TOF-ESI-MS *m/z* (rel int): 385 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{20}H_{21}N_2O_6$ 385.1400; found 385.1388.

43{3,1,1} HPLC: $t_R = 3.184$ min. TOF-ESI-MS *m/z* (rel int): 397 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{22}H_{25}N_2O_5$ 397.1763; found 397.1781.

43{4,1,1} HPLC: $t_R = 2.696$ min. TOF-ESI-MS *m/z* (rel int): 408 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{22}H_{22}N_3O_5$ 408.1559; found 408.1539.

43{5,1,1} HPLC: $t_R = 3.190$ min. TOF-ESI-MS *m/z* (rel int): 417 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{24}H_{21}N_2O_5$ 417.1450; found 417.1429.

43{6,1,1} HPLC: t_R = 3.214 min. TOF-ESI-MS *m/z* (rel int): 431 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{25}H_{23}N_2O_5$ 431.1607; found 431.1584.

43{7,1,1} HPLC: t_R = 2.741 min. TOF-ESI-MS *m/z* (rel int): 443 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{16}H_{16}IN_2O_5$ 443.0104; found 443.0107.

43{8,1,1} HPLC: t_R = 3.467 min. TOF-ESI-MS *m/z* (rel int): 449 ($[M+H]^+$, 38). HR-TOF-ESI-MS *m/z* calcd for $C_{26}H_{29}N_2O_5$ 449.2076; found 449.2055.

43{1,8,1} HPLC: t_R = 3.023 min. TOF-ESI-MS *m/z* (rel int): 548 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{30}H_{34}N_3O_7$ 548.2397; found 548.2369.

43{2,8,1} HPLC: t_R = 2.664 min. TOF-ESI-MS *m/z* (rel int): 552 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{29}H_{34}N_3O_8$ 552.2346; found 552.2320.

43{3,8,1} HPLC: t_R = 3.147 min. TOF-ESI-MS *m/z* (rel int): 564 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{31}H_{38}N_3O_7$ 564.2710; found 564.2730.

43{4,8,1} HPLC: t_R = 2.726 min. TOF-ESI-MS *m/z* (rel int): 575 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{31}H_{35}N_4O_7$ 575.2506; found 575.2524.

43{5,8,1} HPLC: t_R = 3.174 min. TOF-ESI-MS *m/z* (rel int): 584 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{33}H_{34}N_3O_7$ 584.2397; found 584.2416.

43{6,8,1} HPLC: t_R = 3.172 min. TOF-ESI-MS *m/z* (rel int): 598 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{34}H_{36}N_3O_7$ 598.2553; found 598.2546.

43{7,8,1} HPLC: t_R = 2.768 min. TOF-ESI-MS *m/z* (rel int): 610 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{25}H_{29}IN_3O_7$ 610.1050; found 610.1064.

43{8,8,1} HPLC: t_R = 3.450 min. TOF-ESI-MS *m/z* (rel int): 616 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{35}H_{42}N_3O_7$ 616.3023; found 616.3010.

43{1,8,3} HPLC: t_R = 3.074 min. TOF-ESI-MS *m/z* (rel int): 620 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{33}H_{38}N_3O_9$ 620.2608; found 620.2621.

43{2,8,3} HPLC: t_R = 2.764 min. TOF-ESI-MS *m/z* (rel int): 624 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{32}H_{38}N_3O_{10}$ 624.2557; found 624.2554.

43{3,8,3} HPLC: t_R = 3.235 min. TOF-ESI-MS *m/z* (rel int): 636 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{31}H_{42}N_3O_9$ 636.2921; found 636.2899.

43{4,8,3} HPLC: t_R = 2.812 min. TOF-ESI-MS *m/z* (rel int): 647 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{34}H_{39}N_4O_9$ 647.2717; found 647.2700.

43{5,8,3} HPLC: t_R = 3.241 min. TOF-ESI-MS *m/z* (rel int): 656 ($[M+H]^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{36}H_{36}N_3O_9$ 656.2608; found 656.2615.

43{6,8,3} HPLC: t_R = 3.249 min. TOF-ESI-MS *m/z* (rel int): 670 ([M+H]$^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{37}H_{40}N_3O_9$ 670.2765; found 670.2777.

43{7,8,3} HPLC: t_R = 2.857 min. TOF-ESI-MS *m/z* (rel int): 682 ([M+H]$^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{28}H_{33}IN_3O_9$ 682.1262; found 682.1285.

43{8,8,3} HPLC: t_R = 3.488 min. TOF-ESI-MS *m/z* (rel int): 688 ([M+H]$^+$, 100). HR-TOF-ESI-MS *m/z* calcd for $C_{38}H_{46}N_3O_9$ 688.3234; found 688.3226.

Test Library Photolysis for Biological Assays. 3-Alkynylbenzyl amido acyl tricycle-Anp-TentaGel resins **43R{X,X,1}** through **43R{X,X,8}** prepared above (10 mg, 0.24 meq/g avg, 2.37 μmol avg) were placed in Eppendorf tubes, swollen in 120 μL CH_3CN, and photolyzed for 90 min. The resins were filtered through BioSpin® columns and rinsed with an additional 2 × 60 μL CH_3CN. The filtrates were concentrated for 30 min on a SpeedVac at Low Drying Rate. The samples were redissolved in 18.5 μL DMSO at an estimated average concentration of 1 mM per compound, assuming 50% photocleavage yield. These stock solutions were used in assays for suppression of rapamycin-based growth inhibition in *S. cerevisiae*, modulation of the cyclin B degradation pathway in a *Xenopus laevis* oocyte extract assay, inhibition of mink lung cell proliferation (see Experimentals herein), and activation of a TGF-β-responsive reporter gene (see Experimentals herein).

3-Alkynylbenzyl amido 2-methoxyacetyl tricycle-Anp-TentaGel resins **43R{X,1,3}** through **43R{X,8,3}** and 3-alkynylbenzyl amido methylterephthaloyl tricycle-Anp-TentaGel resins **43R{X,1,8}** through **43R{X,8,8}** prepared above (3-4 mg, 0.23-0.25 meq/g, 0.7-2.0 μmol) were weighed into Eppendorf tubes and swollen with 50 μL CH_3CN. After 2 h photolysis, the resins were filtered through BioSpin® columns and rinsed with an additional 2 × 100 μL CH_3CN. The filtrates were concentrated as above and redissolved in 43-62 μL DMSO at an estimated concentration of 1 mM per compound, assuming 50% photocleavage yield. These stock solutions were used in the TGF-β-responsive reporter gene assay.

3-Alkynylbenzyl tetracycle-Anp-TentaGel resins **43R{1,1,1}** through **43R{8,1,1}** (50 mg, 0.25 meq/g avg, 12.38 μmol avg), 3-alkynylbenzyl veratrylamido hydroxy tricycle-Anp-TentaGel resins **43R{1,8,1}** through **43R{8,8,1}** (50 mg, 0.24 meq/g avg, 11.89 μmol avg), and 3-alkynylbenzyl veratrylamido 2-methoxyacetyl tricycle-Anp-TentaGel resins **43R{1,8,3}** through **43R{8,8,3}** prepared above (41-47 mg, 0.23 meq/g avg, 10.23 μmol avg) were placed in two Eppendorf tubes per sample. The resin in each tube was swollen with 400 μL CH_3CN and photolyzed for 2 h. 20 μL of each sample was removed for HPLC and LC-MS analysis. The remainder of each sample was filtered through a BioSpin® column and rinsed with CH_3CN. The

filtrates were concentrated by rotary evaporation in tared 4 mL glass vials. The residue was redissolved in 888.9 μL CD_3CN. 800 μL was used for NMR analysis and set aside. The remaining 88.9 μL of each sample was concentrated for 15 min on a SpeedVac at Low Drying Rate and redissolved in 61.9, 59.4, or 51.1 μL DMSO at an estimated average concentration of 10 mM per compound, assuming 50% photocleavage yield. These stock solutions were used in the TGF-β-responsive reporter gene assay.

After initial screening, the six active compounds were recovered from the NMR samples and purified by silica gel chromatography (CH_2Cl_2/THF) to yield the pure products **43{5,1,1}**, **43{6,1,1}**, **43{5,8,1}**, **43{6,8,1}**, **43{5,8,3}**, and **43{6,8,3}** (0.5-0.8 mg, 7-12%) as clear residues. The purified products were dissolved in DMSO at a concentration of 20 mM and retested in the TGF-β-responsive reporter gene assay.

VI. Full-Scale Library Synthesis and Tagging

Full-Scale Library – General. Spacer, epoxycyclohexenol, iodobenzyl nitrone carboxylic acid, alkyne, amine, and acid building blocks included in full-scale library synthesis are listed below (Tables G-J). Pooling steps were performed by rinsing all resin portions into a silanized 50 mL fritted glass tube followed by thorough mixing by N_2 bubbling in CH_2Cl_2. The resin was then slurried in CH_2Cl_2 and transferred via Gilson P5000 pipetteman to a PD-10 column (placed under high vacuum for 30 min then tared) with drainage provided by a VacMan manifold. The resin was washed several times with distd CH_2Cl_2, allowed to dry several minutes by drawing air through the tube, then washed down with additional distd CH_2Cl_2. The entire tube was then placed under high vacuum for 30 min and reweighed. Splitting steps were accomplished by weighing aliquots of the pooled resin into the appropriate vessels. The last portion of resin was removed from the pooling tube via vacuum cannula transfer to the appropriate vessel.

Tagging reactions were performed before each building block coupling step. Beads from every portion of the library were analyzed to verify tag coupling. The binary tagging code is shown below (Table K). A representative sample of the EC-GC data is shown below (Figure 68). Complete EC-GC data (165 pages) have been obtained.

Alkyne, amine, and acid coupling reactions were performed in sets of seven to facilitate washing after the reactions. PD-10 and BioSpin® columns were capped at both ends and sealed with teflon tape and parafilm.

Full-Scale Library – Spacer resins (37R). In each of six PD-10 columns was placed H_2N-Anp-TentaGel **36R** (416.7 mg, 114.4 μmol, 1.0 equiv). After tagging, to two each of the six resin portions was added Fmoc-Gly-OH (102 mg, 343.2 μmol, 3.0 equiv) or Fmoc-Aca-OH

(121 mg, 343.2 μmol, 3.0 equiv). The remaining two portions were set aside as the R_1 skip codon. PyBOP (179 mg, 343.2 μmol, 3.0 equiv) was added to each of the four tubes being coupled. NMP (5 mL) and DIPEA (99.6 μL, 572.0 μmol, 5.0 equiv) were then added to each tube with brief vortexing between each addition. After mixing for 80 min, the resin portions were washed with 5 × NMP, 5 × CH_2Cl_2 and a small sample of each treated with the Kaiser ninhydrin test to verify complete coupling. The portions were then treated with 20% piperidine in DMF for 2 × 15 min and washed as above. The deprotection reaction was verified by Kaiser ninhydrin test.

Full-Scale Library – Epoxycyclohexenol resins (38R). After pooling, the spacer-containing resins, **37R**, were split into two equal portions in silanized 50 mL fritted glass tubes and tagged. Both of the resin portions (1.25 g, 0.27 meq/g avg, 337.5 μmol, 1.0 equiv) were then washed with 1 × 20% DIPEA in CH_2Cl_2, 3 × CH_2Cl_2, and 1 × anhyd NMP. The resin was bubbled in minimal distd CH_2Cl_2 and the appropriate epoxycyclohexenol carboxylic acid, 7 (58 mg, 371.3 μmol, 1.1 equiv) and PyBOP (193.2 mg, 371.3 μmol, 1.1 equiv) were added to each vessel, followed by NMP (25 mL). DIPEA (176.4 μL, 1.01 mmol, 3.0 equiv) was added to each tube and the reactions were allowed to proceed with N_2 bubbling for 9 h. The resins were washed with 5 × NMP and 5 × CH_2Cl_2 and complete conversion was verified by Kaiser ninhydrin test.

Full-Scale Library – Iodobenzyl tetracycle resins (39R). After pooling, the epoxycyclohexenol-containing resins, **38R**, were split into six equal portions in PD-10 columns and tagged. To two each of the six tagged resin portions (429 mg, 0.26 meq/g avg, 111.8 μmol, 1.0 equiv, dried under high vacuum) were added the appropriate nitrone carboxylic acid, **11** (68.2 mg, 223.6 μmol, 2.0 equiv) and PyBroP (104.2 mg, 223.6 μmol, 2.0 equiv). The tubes were flushed with Ar and cooled to 0 °C in an ice bath. CH_2Cl_2 (4 mL), DIPEA (77.9 μL, 447.2 μmol, 4.0 equiv), and solid DMAP (15.0 mg, 123.0 μmol, 1.1 equiv) were added in sequence with immediate vortexing and recooling to 0 °C between each addition. The tubes were transferred to a Labquake in a 4 °C cold cabinet for 2 h, then mixed at rt for 2-10 h. After the standard wash (Method B), approx 1 mg of resin was removed from each tube and photolyzed in 30 μL CH_3CN for 2 h. Percent conversion was analyzed by TLC (17:3 CH_2Cl_2/MeOH and 1:1 CH_2Cl_2/THF). The process was repeated until no epoxycyclohexenol carboxamides, **38**, could be detected. LC-MS analysis of photocleaved samples from each of the six pools indicated the presence of all three of the expected tetracycles, **39**, in each pool.

Full-Scale Library – Alkynylbenzyl tetracycle resins (40R). After pooling, the iodobenzyl tetracycle-containing resins, 39R, were split into 31 equal porti ns in 2 mL BioSpin® columns and tagged. To each tagged resin portion (86 mg, 0.24 meq/g, 20.85 μmol, 1.0 equiv) was added copper(I) iodide (8.7 mg, 45.87 μmol, 2.2 equiv) and bis(triphenylphosphine)palladium(II) chloride (16.1 mg, 22.94 μmol, 1.1 equiv) or tetrakis(triphenylphosphine)palladium(0) (26.5 mg, 22.94 μmol, 1.1 equiv). DMF (860 μL) was added and the tubes were flushed with Ar and vortexed briefly. DIPEA (monoynes: 109 μL, 625.5 μmol, 30 equiv; diynes: 254.3 μL, 1.460 mmol, 70 equiv) was added followed immediately by the appropriate alkyne (monoynes: 417 μmol, 20 equiv; diynes 1.043 mmol, 50 equiv). The tubes were vortexed briefly and mixed for 2 h followed by the standard wash procedure (Method B).

Full-Scale Library – Alkynylbenzyl amido hydroxy tricycle resins (41R). After pooling, the alkynylbenzyl tetracycle-containing resins, 40R, were split into 63 portions in 2 mL BioSpin® columns such that the 63rd (aminolysis skip codon) portion was 1/63rd the weight of the other equal 62 portions. Following tag coupling, the 63rd portion was set aside and to each of the remaining resin portions (40.45 mg, 0.24 meq/g, 9.82 μmol, 1.0 equiv) was added 2-hydroxypyridine (non-α-branched amines: 4.67 mg, 49.09 μmol, 5 equiv; α-branched amines:, 9.34 mg, 98.17 μmol, 10 equiv) as a 404.5 μL stock solution in THF (free amines) or 3:2 CH_2Cl_2/DMF (amine hydrochloride salts). The tubes were flushed with Ar and the appropriate amine (non-α-branched amines: 245.43 μmol, 25 equiv; α-branched amines 490.86 μmol, 50 equiv) was added to each tube followed by DIPEA (85.5 μL, 490.86 μmol, 50 equiv) where appropriate. The tubes were vortexed briefly and mixed for 15 h followed by the standard wash procedure (Method A).

Full-Scale Library – Alkynylbenzyl amido acyl tricycle resins (42R). The first 62 alkynylbenzyl γ-hydroxyamido tricycle-containing resin portions, 41R, above were pooled and split into 63 equal portions in 2 mL BioSpin® columns and tagged. The 63rd (aminolysis skip codon) portion above was set aside. After tagging, to each of the resin portions (37.14 mg, 0.235 meq/g, 8.72 μmol, 1.0 equiv) was added 150 μL CH_2Cl_2. The tubes were flushed with Ar and cooled to 0 °C in an ice bath. The appropriate acids (871.8 μmol, 100 equiv) were placed in oven-dried 8 mL teflon-capped vials and dissolved in 532 μL CH_2Cl_2. DIPC (68.5 μL, 435.9 μmol, 50 equiv) was added and the mixture was stirred for 2 min. DIPEA (75.9 μL, 435.9 μmol, 50 equiv) was added and the mixture was stirred another 3 min. *Half* of each preactivated acid mixture was added to the appropriate BioSpin® column. Each tube was vortexed briefly and

returned to 0 °C. DMAP (5.325 mg, 43.58 μmol, 5 equiv) was added to each tube as a 50 μL stock solution in CH_2Cl_2, and the tubes were wrapped with parafilm, vortexed briefly, and returned to 0 °C for 30 min. The tubes were warmed to rt and mixed for 11 h followed by the standard wash procedure (Method A) with an additional 3 × 20% DIPEA in CH_2Cl_2 wash. The 63 acylated resins and the lactone aminolysis skip codon resin were then combined to yield the completed full-scale library, **42R**, as a brown resin.

VII. Encoding Methods and Biological Testing:

Binary Encoding – General. HPLC grade CH_3CN, spectrophotometric grade DMF, and 99+% decane (Aldrich) were used in bead picking and tag cleavage procedures. DMF and decane were stored over activated 4Å MS during use. *N,O*-Bistrimethylsilylacetamide (BSA, Pierce, Rockford, IL; 38836) was obtained in ampules and stored as stocks at -20 °C. Solvent and BSA aliquots were prepared fresh daily. Ammonium cerium nitrate (CAN, Aldrich, 136 mg) was dissolved in 0.5 mL distd THF and 0.5 mL ddH_2O and used within 2 h of preparation. Sonication was performed in an Ultrasonic Cleaner water bath (Cole-Parmer, Vernon Hills, IL; 8892). Centrifugation was performed at 2000 × g with a National Labnet C-1200 Mini Centrifuge (VWR 20668-212). EC-GC analysis was performed on a Hewlett-Packard 5890E Series II Plus gas chromatograph equipped with an Ultra-1 crosslinked methyl siloxane 25 m x 0.2 mm x 0.33 μm film thickness capillary column (HP 19091A-102) and a ^{63}Ni electron capture detector (HP 19233-69576).

Binary Encoding – Tag Coupling. The resin to be tagged was washed with 5 × distd CH_2Cl_2. Resins containing free amine functionalities were washed further with 5 × 0.2% TFA in distd CH_2Cl_2. Rhodium triphenylacetate prepared as previously described (Callot et al. *Tetrahedron* **1985**, *41*, 4495) (180 nmol per 100 mg resin) was dissolved in distd EtOAc (1 mL per 100 mg resin) by sonication for 20 sec and added to the resin. The mixture was agitated for 10 min by N_2 bubbling, 360° rotation, or gentle vortexing as appropriate for the reaction vessel. The diazoketone tags synthesized as previously described (Ohlmeyer et al. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10922; Nestler et al. *J. Org. Chem.* **1994**, *59*, 4723) were dissolved in EtOAc at a concentration of approximately 24 mM. The appropriate stock solutions (500 μL per 100 mg resin) were combined to generate the binary code for each building block (see Supporting Information). The combined stock solution was added to the resin in four equal portions at 30 min intervals. 2 h after the final addition, the resin was drained and the procedure repeated. The second coupling reaction was all wed to proceed overnight, then the resin was washed with 5 × CH_2Cl_2 and 5 × CH_3CN.

Binary Encoding – Tag Cleavage and Analysis. Several beads were removed from each reaction tube with the aid of a flame-pulled capillary tube and placed on a glass 25 x 75 mm microscope slide (VWR 48300-025). CH_3CN was added to the plate and a "Microliter 705" 50 μL syringe (Hamilton, Reno, NV; 80530) with a 22s gauge removeable needle (Hamilton 80464) was used to pick single beads with the aid of an Olympus CK2 microscope. The beads were transferred to 1.1-1.2 I.D. x 100 mm glass capillary tubes (Corning, Corning, NY; 9530-2) which had been cut to approximately 3 cm. The tubes were centrifuged briefly, the CH_3CN was removed with a "Microliter 701" 10 μL syringe (Hamilton 80330) with a stainless steel taper needle for 320 μm columns (HP 5182-0831), and the tubes were centrifuged again. 2 μL CAN solution then 3 μL decane were added with centrifugation after each addition. The tubes were allowed to stand for 10 min, sonicated for 1 min, then centrifuged. The 10 μL syringe was rinsed with 3 × CH_3CN, 3 × DMF, 3 × decane, and 2 μL neat BSA. The syringe barrel was coated with the BSA plug, which was then ejected. The top decane layer from the capillary tube was drawn into the syringe and the sample plug drawn up and down in the BSA-coated portion of the barrel. The sample was allowed to stand for 1 min inside the syringe, then analyzed by EC-GC using the published method (Ohlmeyer et al. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10922) EC-GC analysis of single bead cleavage samples from all tagged resin portions indicated satisfactory tag incorporation with clearly defined peaks.

Cell Proliferation Assay. 10,000 Mv1Lu mink lung epithelial cells were seeded in each well of a 12-well dish in 1 mL Dubelco's Modified Eagle Medium (DMEM, GibcoBRL, Gaithersburg, MD; 11995-040) containing 10% fetal bovine serum (FBS, GibcoBRL 10438-026), 100 units/mL penicillin G sodium (GibcoBRL 15140-122), 100 μg/mL streptomycin sulfate (GibcoBRL 15140-122), and 100 μg/mL each of Ala, Asp, Glu, Gly, Asn, Pro (Sigma, St. Louis, MO or ICN Biomedicals, Aurora, OH). After 24 h, 1 μL of DMSO was added to the DMSO control wells, and 1 μL of 1 mM **43{X,X,1}** through **43{X,X,8}** in DMSO was added to the assay wells. After 4 days, no cell death was observed. The cells were washed with Hanks Balanced Salt Solution (HBSS, GibcoBRL 24020-117), trypsinized, and counted. Experiments were performed in triplicate.

TGF-β-Responsive Reporter Gene Assay. Transforming growth factor beta (TGF-β, Sigma T-1654) was stored in 20 μL aliquots at –80 °C as 40 nM stock solutions (100-1000X) in 0.2 μm-filtered 4 mM HCl with 1 mg/mL bovine serum albumin (Sigma A2153). The plasmid p3TPLux, which contains three copies of the phorbol myristate acetate response element from the collagenase gene as well as a fragment of the plasminogen activator inhibitor type 1 (PAI-1) promoter, was obtained from Joan Massague (Carcamo et al. *J. Mol. Cell. Biol.* **1995**, *15*, 1573)

Mv1Lu mink lung epithelial cells were obtained from the American Type Culture Collection (Manassas, VA; CCL64). 6F mink lung cells, a stably-transfected clone containing p3TPLux as well as another plasmid, are derived from Mv1Lu cells. The generation of this clone was described previously (Stockwell et al. *Curr. Biol.* **1998**, *8*, 761). Both Mv1Lu and 6F cells were cultured in 10% mink medium, which consists of DMEM with 10% FBS, 100 units/mL penicillin G sodium, 100 μg/mL streptomycin sulfate and 100 μM each of Ala, Asp, Glu, Gly, Asn, Pro. 700 μg/mL G418 sulfate (GibcoBRL 11811-031) was added to cultures of 6F cells.

The initial pools **43{X,X,1}** through **43{X,X,8}** were assayed using a previously described scintillation counter method (Stockwell et al. *Chem. Biol.* **1998**, *5*, 385). Deconvoluted pools **43{X,1,3}** through **43{X,8,3}** and **43{X,1,8}** through **43{X,8,8}**, and individual compounds **43{1,1,1}** through **43{8,1,1}**, **43{1,8,1}** through **43{8,8,1}**, and **43{1,8,3}** through **43{8,8,3}** were assayed in 384-well plates as follows: 20,000 6F cells were seeded in 50 μL of 10% mink medium in each well of a white 384-well plate (Nalge Nunc International, Naperville, IL; 164610) using a Multidrop 384 liquid dispenser (Lab Systems, Helsinki, Finland). After 16 hours, medium was removed using a 24 channel wand (V&P Scientific, San Diego, CA; VP186L), the cells were washed with 75 μL of 0.2% mink medium (containing 0.2% FBS), and reagents were added in 40 μL of 0.2% medium. For the primary screen, reagents were added by pin transfer using 384 polypropylene pin arrays (Matrix Technologies, Hudson, NH). After 24 hours, the cells were cooled on ice and washed twice with 75 μL HBSS. Then 20 μL lysis buffer (25 mM glycylglycine (Sigma G7278) pH 7.8, 15 mM $MgSO_4$ (Sigma M5921), 4 mM EGTA (Sigma E0396), 1% Triton X-100 (Sigma T9284), 1 mM dithiothreitol (DTT, Sigma D5545), 1 mM phenylmethylsulfonyl fluoride (Sigma P7626)) was added to each well with a Multidrop dispenser. After incubating the cells for five minutes on ice, 20 μL of ATP/luciferin solution was added (25 mM glycylglycine pH 7.8, 15 mM $MgSO_4$, 4 mM EGTA, 6.25 mM K_2HPO_4 (Sigma P5504) pH 7.8, 5 mM DTT, 75 μM D-luciferin (Sigma L9504), 2 mM ATP (Sigma A7699)). Light output was immediately measured with an LJL Analyst 384-well platereader, with 0.5 s counting time per well.

Table A.	Alkyne building blocks tested.									
			mono terminal alkynes	47.84	umol alkyne (20 eq)					
			bis terminal alkynes (italicized)	119.60	umol alkyne (50 eq)					
Test				mg or uL			√ = ≥90% conversion & purity			
#	Vendor	Catalog #	Chemical Name	alkyne	MW	d	HPLC	Mass	LCMS	TLC
±1	Aldrich	33,482-0	Acetaldehyde ethyl propargyl acetal	6.83	128.17	0.898	50%	555	60%	
±2	Aldrich	38,425-9	Butyl 1-methyl-2-propynyl ether, tert-	7.59	126.20	0.795	√	553	√	
3	GFS	115730	Butyl)phenylacetylene, 4-(tert-	8.50	158.00	0.889	80%	585	√	
4	Aldrich	39,926-4	Butyldimethylsilyl)acetylene, (tert-	8.94	140.30	0.751	50%	567	50%	
±5	Aldrich	30,586-3	Butynloxy)tetrahydro-2H-pyran, 2-(3-	7.50	154.21	0.984	NR	581	NR	50%c
6	Aldrich	20,647-4	Chloro-4-ethynylbenzene, 1-	6.53	136.58	1.000	√	564	√	
7	GFS	126504	Decadiyne (50% in hexane), 1,4-	12.84	134.22	0.500	20%	561	20%	
8	GFS	126706	Decadiyne, 1,5-	6.42	134.22	1.000	√	561	√	
9	GFS	129103	Dibutylamino-1-propyne, 3-	6.61	111.19	0.804	NR	538	NR	
10	*GFS*	*130100*	*Diethynylbenzene, m-*	*15.09*	*126.15*	*1.000*	*60%*	553	*80%*	
11	Aldrich	24,439-2	Dimethyl-1-butyne, 3,3-	5.89	82.15	0.667	√	509	√	
12	Aldrich	14,306-5	Dimethylamino-2-propyne, 1-	5.15	83.13	0.772	50%	510	10%	80%c
13	Aldrich	24,440-6	Dodecyne, 1-	10.23	166.31	0.778	80%	593	90%	
14	Aldrich	27,136-5	Ethyl ethynyl ether (50% in hexanes)	6.71	70.09	0.500	NR	497	NR	
15	Aldrich	41,986-9	Ethynyl p-tolyl sulfone	8.62	180.23	1.000	NR	607	NR	
16	Aldrich	40,433-0	Ethynyl-4-fluorobenzene, 1-	5.48	120.13	1.048	n.d.	547	n.d.	
17	Aldrich	31,657-1	Ethynylcyclohexene, 1-	5.62	106.17	0.903	√	533	√	
18	Aldrich	85,587-1	Ethynylestradiol 3-methyl ether	14.85	310.44	1.000	√	737	√	
19	GFS	143907	Ethynylpyridine, 2-	5.25	103.12	0.940	NR	530	50%	70%c
20	Aldrich	20,650-4	Ethynyltoluene, 4-	6.07	116.16	0.916	√	543	√	
21	*Aldrich*	*40,729-1*	*Hexadiyne (50% in hexane), 1,5-*	*18.68*	*78.11*	*0.500*	*30%*	505	*40%*	
22	Aldrich	24,442-2	Hexyne, 1-	5.50	82.15	0.715	√	509	√	
23	Aldrich	27,134-9	Hexynenitrile, 5-	5.01	93.13	0.889	√	520	√	
24	Aldrich	17,719-9	Methyl propargyl ether	4.04	70.09	0.830	70%	497	80%	
25	Aldrich	M3,280-1	Methyl-1-buten-3-yne, 2-	4.55	66.10	0.695	√	493	√	
26	Aldrich	M7,425-3	Methyl-N-propargylbenzylamine, N-	8.07	159.23	0.944	√	586	√	90%c
27	*Aldrich*	*16,130-6*	*Nonadiyne, 1,8-*	*17.99*	*120.20*	*0.799*	*nuked*	547	*nuked*	*baseline*
28	Aldrich	25,656-0	Pentyne, 1-	[illegible]	68.12	0.691	√	495	√	

Table A.		Alkyne building blocks tested.								
			mono terminal alkynes	47.84	umol alkyne (20 eq)					
			bis terminal alkynes (italicized)	119.60	umol alkyne (50 eq)					
							√ = ≥90% conversion & purity			
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±2	Aldrich	38,425-9	Butyl 1-methyl-2-propynyl ether, tert-	7.59	126.20	0.795	√	553	√	
3	GFS	115730	Butyl)phenylacetylene, 4-(tert-	8.50	158.00	0.889	80%	585	√	
4	Aldrich	39,926-4	Butyldimethylsilyl)acetylene, (tert-	8.94	140.30	0.751	50%	567	50%	
±5	Aldrich	30,586-3	Butynloxy)tetrahydro-2H-pyran, 2-(3-	7.50	154.21	0.984	NR	581	NR	50%c
6	Aldrich	20,647-4	Chloro-4-ethynylbenzene, 1-	6.53	136.58	1.000	√	564	√	
7	GFS	126504	Decadiyne (50% in hexane), 1,4-	12.84	134.22	0.500	20%	561	20%	
				[illegible]						
8	GFS	126706	Decadiyne, 1,5-	6.42	134.22	1.000	√	561	√	
9	GFS	129103	Dibutylamino-1-propyne, 3-	6.61	111.19	0.804	NR	538	NR	
10	*GFS*	*130100*	*Diethynylbenzene, m-*	*15.09*	*126.15*	*1.000*	*60%*	553	*80%*	
11	Aldrich	24,439-2	Dimethyl-1-butyne, 3,3-	5.89	82.15	0.667	√	509	√	
12	Aldrich	14,306-5	Dimethylamino-2-propyne, 1-	5.16	83.13	0.772	50%	510	10%	80%c
13	Aldrich	24,440-6	Dodecyne, 1-	10.23	166.31	0.778	80%	593	90%	
14	Aldrich	27,136-5	Ethyl ethynyl ether (50% in hexanes)	6.71	70.09	0.500	NR	497	NR	
				[illegible]						
15	Aldrich	41,986-9	Ethynyl p-tolyl sulfone	8.62	180.23	1.000	NR	607	NR	
16	Aldrich	40,433-0	Ethynyl-4-fluorobenzene, 1-	5.48	120.13	1.048	n.d.	547	n.d.	
17	Aldrich	31,657-1	Ethynylcyclohexene, 1-	5.62	106.17	0.903	√	533	√	
18	Aldrich	85,587-1	Ethynylestradiol 3-methyl ether	14.85	310.44	1.000	√	737	√	
19	GFS	143907	Ethynylpyridine, 2-	5.25	103.12	0.940	NR	530	50%	70%c
20	Aldrich	20,650-4	Ethynyltoluene, 4-	6.07	116.16	0.916	√	543	√	
21	*Aldrich*	*40,729-1*	*Hexadiyne (50% in hexane), 1,5-*	*18.68*	*78.11*	*0.500*	*30%*	505	*40%*	
22	Aldrich	24,442-2	Hexyne, 1-	5.50	82.15	0.715	√	509	√	
23	Aldrich	27,134-9	Hexynenitrile, 5-	5.01	93.13	0.889	√	520	√	
24	Aldrich	17,719-9	Methyl propargyl ether	4.04	70.09	0.830	70%	497	80%	
25	Aldrich	M3,280-1	Methyl-1-buten-3-yne, 2-	4.55	66.10	0.695	√	493	√	
26	Aldrich	M7,425-3	Methyl-N-propargylbenzylamine, N-	8.07	159.23	0.944	√	586	√	90%c
27	*Aldrich*	*16,130-6*	*Nonadiyne, 1,8-*	*17.99*	*120.20*	*0.799*	*nuked*	547	*nuked*	*baseline*
28	Aldrich	25,656-0	Pentyne, 1-	[illegible]	68.12	0.891	√	495	√	

Table A.			Alkyne building blocks tested.							
			mono terminal alkynes	47.84	umol alkyne (20 eq)					
			bis terminal alkynes (italicized)	119.60	umol alkyne (50 eq)					
Test				mg or uL			√ = ≥90% conversion & purity			
#	Vendor	Catalog #	Chemical Name	alkyne	MW	d	HPLC	Mass	LCMS	TLC
±1	Aldrich	33,482-0	Acetaldehyde ethyl propargyl acetal	6.83	128.17	0.898	50%	555	60%	
±2	Aldrich	38,425-9	Butyl 1-methyl-2-propynyl ether, tert-	7.59	126.20	0.795	√	553	√	
3	GFS	115730	Butyl)phenylacetylene, 4-(tert-	6.50	158.00	0.889	80%	585	√	
4	Aldrich	39,926-4	Butyldimethylsilyl)acetylene, (tert-	6.94	140.30	0.751	50%	567	50%	
±5	Aldrich	30,586-3	Butynloxy)tetrahydro-2H-pyran, 2-(3-	7.50	154.21	0.984	NR	581	NR	50%c
6	Aldrich	20,647-4	Chloro-4-ethynylbenzene, 1-	6.53	136.58	1.000	√	564	√	
7	GFS	126504	Decadiyne (50% in hexane), 1,4-	12.64	134.22	0.500	20%	561	20%	
8	GFS	126706	Decadiyne, 1,5-	6.42	134.22	1.000	√	561	√	
9	GFS	129103	Dibutylamino-1-propyne, 3-	6.61	111.19	0.804	NR	538	NR	
10	*GFS*	*130100*	*Diethynylbenzene, m-*	*15.09*	*126.15*	*1.000*	*60%*	553	*80%*	
11	Aldrich	24,439-2	Dimethyl-1-butyne, 3,3-	5.89	82.15	0.667	√	509	√	
12	Aldrich	14,306-5	Dimethylamino-2-propyne, 1-	5.15	83.13	0.772	50%	510	10%	80%c
13	Aldrich	24,440-6	Dodecyne, 1-	10.23	166.31	0.778	80%	593	90%	
14	Aldrich	27,136-5	Ethyl ethynyl ether (50% in hexanes)	6.71	70.09	0.500	NR	497	NR	
15	Aldrich	41,986-9	Ethynyl p-tolyl sulfone	8.62	180.23	1.000	NR	607	NR	
16	Aldrich	40,433-0	Ethynyl-4-fluorobenzene, 1-	5.48	120.13	1.048	n.d.	547	n.d.	
17	Aldrich	31,657-1	Ethynylcyclohexene, 1-	5.62	106.17	0.903	√	533	√	
18	Aldrich	85,587-1	Ethynylestradiol 3-methyl ether	14.85	310.44	1.000	√	737	√	
19	GFS	143907	Ethynylpyridine, 2-	5.25	103.12	0.940	NR	530	50%	70%c
20	Aldrich	20,650-4	Ethynyltoluene, 4-	6.07	116.16	0.916	√	543	√	
21	*Aldrich*	*40,729-1*	*Hexadiyne (50% in hexane), 1,5-*	*18.68*	*78.11*	*0.500*	*30%*	505	*40%*	
22	Aldrich	24,442-2	Hexyne, 1-	5.50	82.15	0.715	√	509	√	
23	Aldrich	27,134-9	Hexynenitrile, 5-	5.01	93.13	0.889	√	520	√	
24	Aldrich	17,719-9	Methyl propargyl ether	4.04	70.09	0.830	70%	497	80%	
25	Aldrich	M3,280-1	Methyl-1-buten-3-yne, 2-	4.66	66.10	0.695	√	493	√	
26	Aldrich	M7,425-3	Methyl-N-propargylbenzylamine, N-	8.07	159.23	0.944	√	586	√	90%c
27	*Aldrich*	*16,130-6*	*Nonadiyne, 1,8-*	*17.99*	*120.20*	*0.799*	*nuked*	547	*nuked*	*baseline*
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9	GFS	129103	Dibutylamino-1-propyne, 3-	6.61	111.19	0.804	NR	538	NR	
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12	Aldrich	14,306-5	Dimethylamino-2-propyne, 1-	5.15	83.13	0.772	50%	510	10%	80%c
13	Aldrich	24,440-6	Dodecyne, 1-	10.23	166.31	0.778	80%	593	90%	
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30	Aldrich	37,684-1	Phenyl-1-propyne, 3-	5.95	116.16	0.934	√	543	√	
31	Aldrich	11,770-6	Phenylacetylene	5.25	102.14	0.930	√	529	√	
32	*Aldrich*	*41,696-7*	*Propargyl ether*	12.37	*94.11*	*0.914*	*NR*	521	*30%*	
33	Aldrich	44,694-7	Propargyl-1H-benzotriazole, 1-	7.52	157.18	1.000	30%	584	10%	
34	Aldrich	P5,133-8	Propargyloxy)phthalimide, N-(	9.62	201.18	1.000	NR	628	10%	
35	GFS	187530	Propargylphthalimide, N-	8.86	185.18	1.000	40%	612	30%	
36	Aldrich	22,648-3	Propargyltriphenylphosponium bromide	18.24	381.26	1.000	NR	808	NR	
37	Aldrich	30,360-7	Propiolaldehyde diethyl acetal	6.86	128.17	0.894	NR	555	NR	
±38	Aldrich	30,081-0	Tetrahydro-2-(2-propynyloxy)-2H-pyran	6.73	140.18	0.997	40%	567	40%	
39	Aldrich	34,697-7	Triethylsilyl)acetylene, (	8.57	140.30	0.783	70%	567	80%	
40	GFS	193080	Trimethylsilyl-1,4-pentadiyne, 1-	6.52	136.27	1.000	NR	563	20%	
41	Aldrich	36,005-8	Triphenylsilyl)acetylene, (	13.61	284.44	1.000	40%	711	40%	
42	*Aldrich*	*T8,496-4*	*Tripropargylamine*	25.39	*131.18*	*0.927*	*NR*	558	*30%*	
43	Aldrich	30,586-3	Butynloxy)tetrahydro-2H-pyran, 2-(3-	7.50	154.21	0.984	√	581	√	
44	GFS	133502	Dimethyl-1-hexyn-3-ol, 3,5-	6.04	126.20	1.000	√	553	√	
45	GFS	136101	Diphenyl-2-propyn-1-ol, 1,1-	9.96	208.26	1.000	√	635	√	
46	Aldrich	E5,140-6	Ethynyl-1-cyclohexanol, 1-	6.14	124.18	0.967	√/NR?	551	80%p	
47	Aldrich	40,433-0	Ethynyl-4-fluorobenzene, 1-	5.48	120.13	1.048	√	547	√	
48	GFS	143705	Ethynyl-9-fluorenol, 9-	9.87	206.25	1.000	√	633	√	
49	Aldrich	13,086-9	Ethynylcyclopentanol, 1-	5.48	110.16	0.962	√/NR?	537	80%p	
50	Aldrich	24,441-4	Heptyne, 1-	6.26	96.17	0.733	70%c	523	60%c	
51	Aldrich	13,756-1	Methyl-1-pentyn-3-ol, 3-	5.42	98.15	0.866	80%p	525	80%p	
52	GFS	184903	Phenyl-3-butyn-2-ol, 2-	6.99	146.19	1.000	√	573	√	
53	Aldrich	30,360-7	Propiolaldehyde diethyl acetal	6.26	128.17	0.894	40%c	555	40%c	

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29	GFS	184701	Phenyl-1-butyne, 4-	6.73	130.19	0.926	√	557	√	
30	Aldrich	37,684-1	Phenyl-1-propyne, 3-	5.95	116.16	0.934	√	543	√	
31	Aldrich	11,770-6	Phenylacetylene	5.25	102.14	0.930	√	529	√	
32	*Aldrich*	*41,696-7*	*Propargyl ether*	*12.31*	*94.11*	*0.914*	*NR*	521	*30%*	
33	Aldrich	44,684-7	Propargyl-1H-benzotriazole, 1-	7.52	157.18	1.000	30%	584	10%	
34	Aldrich	P5,133-8	Propargyloxy)phthalimide, N-(	9.62	201.18	1.000	NR	628	10%	
35	GFS	187530	Propargylphthalimide, N-	6.86	185.18	1.000	40%	612	30%	
36	Aldrich	22,648-3	Propargyltriphenylphosponium bromide	18.24	381.26	1.000	NR	808	NR	
37	Aldrich	30,360-7	Propiolaldehyde diethyl acetal	6.86	128.17	0.894	NR	555	NR	
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Table B.		Amine building blocks tested.												
		beta-branched or greater (mult = 1)	30.23	umol amine (25 eq)										
		alpha-branched (mult = 2)	60.49	umol amine (50 eq)										
		2-hydroxypyridine (2-pyr) stock solutions	1.0	6.05 umol (5 eq) in THF										
			1.X	6.05 umol (5 eq) in 3:2 CH2Cl2/DMF										
			2.0	12.09 umol (10 eq) in THF										
			2.X	12.09 umol (10 eq) in 3:2 CH2Cl2/DMF										
										√ = ≥90% conversion				FAB
Test	Aldrich			mg or uL	uL				acid		and purity			rel int
#	Catalog #	Chemical Name	2-pyr	amine	DIPEA	MW	d	mult	salt	HPLC	Mass	LCMS	TLC	Pd/SM
1	24,107-5	Allylamine	1.0	2.27		57.10	0.761	1		√	566	√		
2	10,741-7	Amino-1-propene-1,1,3-tricarbonitrile, 2-	2.0	7.99		132.13	1.000	2		NR?	641	NR	NR	
3	41,592-8	Amino-1H-isoindole hydrochloride, 3-	2.1	10.20	21.06	168.63	1.000	2	1	NR?	642	NR	30%?	5/100
4	23,227-0	Amino-5-methylisoxazole, 3-	2.0	5.93		98.10	1.000	2		NR?	607	NR	NR	
5	A3,720-0	Aminoacetaldehyde diethyl acetal	1.0	4.40		133.19	0.916	1		√	642	√		
6	12,196-7	Aminoacetaldehyde dimethyl acetal	1.0	3.29		105.14	0.965	1		√	614	√		
7	13,052-4	Aminoacetonitrile bisulfate	1.1	2.80	10.53	92.53	1.000	1	1	NR?	565	NR	NR?	5/100
8	27,524-7	Aminoethyl)benzenesulfonamide, 4-(2-	1.0	6.05		200.26	1.000	1		√	709	70%		
9	A5,500-4	Aminoethyl)morpholine, 4-(2-	1.0	3.97		130.19	0.992	1		√	639	NR	70%	100/11
10'	A6,540-9	Aminomethyl)pyridine, 2-(2-	1.0	3.08		108.14	1.062	1		√	617	NR	90%	100/2
11	A5,535-7	Aminoethyl)pyrrolidine, 1-(2-	1.0	3.83		114.19	0.901	1		50%	623	NR	70%	100/-
12	A5,952-2	Aminoindan hydrochloride, 2-	2.1	10.26	21.06	169.66	1.000	2	1	NR?	643	20%	40%	
13	44,534-7	Aminoindan, (R)-(-)-1-	2.0	7.76		133.19	1.036	2		√	642	√		
14	44,535-5	Aminoindan, (S)-(+)-1-	2.0	7.76		133.19	1.036	2		√	642	80%		
±15	38,841-6	Aminomethyl)-15-crown-5, 2-(	1.0	6.65		249.31	1.134	1		√	758	70%		
16	A6,180-2	Aminomethyl)benzenesulfonamide hydrochloride, 4-(	1.1	8.73	10.53	222.69	1.000	1	1	40%	695	40%	40%	
17	35,952-1	Aminomethyl)cyclopropane, (	1.0	2.62		71.12	0.820	1		NR?	580	√		
18'	40,163-3	Pyrenemethylamine hydrochloride, 2-	1.1	8.09	10.53	267.76	1.000	1	1	√	740	√	?	
19	A6,540-9	Aminomethyl)pyridine, 3-(	1.0	3.08		108.14	1.062	1		NR?	617	NR	NR	
20	A6,560-3	Aminomethyl)pyridine, 4-(	1.0	3.07		108.14	1.065	1		√	617	nuked	80%	
21	A7,642-7	Aminopropionitrile fumarate, 3-	1.1	3.87	10.53	128.13	1.000	1	1	NR?	579	NR		
22	13,656-5	Aminopropyl)-2-pyrrolidinone, 1-(3-	1.0	4.24		142.20	1.014	1		√	651	√		
23	27,226-4	Aminopropyl)imidazole, 1-(3-	1.0	3.51		125.18	1.049	1		√	634	60%	√?	100/0
24	28,177-8	Aminopropyltrimethoxysilane, 3-	1.0	5.23		179.29	1.027	1		√	688	20%	√?	100/2
25	41,571-5	Aminoquinuclidine dihydrochloride, (R)-(+)-3-	2.2	12.03	42.12	199.14	1.000	2	2	NR?	636	NR	NR	
26	41,572-3	Aminoquinuclidine dihydrochloride, (S)-(-)-3-	2.2	12.04	42.12	199.14	1.000	2	2	NR?	636	NR	NR	
27	40,766-6	Ammonia (0.5M in dioxane)	1.0	60.45		2000	1.000	1		√?	526	NR	NR	-/100
28	18,570-1	Benzylamine	1.0	[illegible]		107.16	0.981	1		NR?	616	√		

Table B.		Amine building blocks tested.												
										√ = ≥90% conversion				FAB
Test	Aldrich			mg or uL	uL				acid		and purity			rel int
#	Catalog #	Chemical Name	2-pyr	amine	DIPEA	MW	d	mult	salt	HPLC	Mass	LCMS	TLC	Pdt/SM
29	40,817-4	Benzylcysteamine hydrochloride, S-	1.1	6.16	10.53	203.74	1.000	1	1	60%	677	50%		
30	35,993-9	Bornylamine, (R)-(+)-	2.0	9.27		153.27	1.000	2		√	662	70%		
31	23,991-7	Butylamine	1.0	2.99		73.14	0.740	1		√	582	√		
32	25,518-5	Cyclobutylamine	2.0	5.16		71.12	0.833	2		√?	580	√		
33	10,184-2	Cyclohexanemethylamine	1.0	[illegible]		113.20	0.870	1		√	622	√		
34	24,064-8	Cyclohexylamine	2.0	6.92		99.18	0.867	2		√	608	√		
35	C11,500-2	Cyclopentylamine	2.0	5.97		85.15	0.863	2		√	594	√		
36	12,550-4	Cyclopropylamine	2.0	4.19		57.10	0.824	2		90%	566	70%		
37	85,857-9	Cycloserine, (R)-(+)-	2.0	6.17		102.09	1.000	2		NR?	611	NR	NR	
38	37,189-0	Diethoxymethylsilyl)propylamine, 3-(	1.0	6.31		191.35	0.916	1		√	700	80%	√	100/0
39	D13,620-4	Dimethoxyphenethylamine, 3,4-	1.0	5.10		181.24	1.074	1		√	690	√		
40	28,583-3	Dimethylamino)benzyamine dihydrochloride, 4-(	1.2	6.75	21.06	223.15	1.000	1	2	NR?	659	NR	NR	–/100
41	24,005-2	Dimethylaminopropylamine, 3-	1.0	3.50		102.18	0.812	1		50%	611	NR	50%	100/2
42	D15,780-5	Dimethylethylenediamine, N,N-	1.0	3.22		88.15	0.828	1		NR	597	NR	50%	0/27
43	39,507-2	Ethylamine (2.0M in THF)	1.0	15.12		500.00	1.000	1		√	554	√		
44	19,019-5	Ethylpropylamine, 1-	2.0	7.05		87.17	0.748	2		√	596	80%		
45	42,905-8	Fluoroethylamine hydrochloride, 2-	1.1	3.01	10.59	99.54	1.000	1	1	80%	573	50%	70%	
46	36,182-8	Fluorophenethylamine, 4-	1.0	3.97		139.17	1.061	1		√	648	√		
47	F2,000-9	Furfurylamine	1.0	2.67		97.12	1.099	1		30%	606	30%	10%	
48	41,264-3	Geranylamine	1.0	5.59		153.27	0.829	1		√	662	√		
49'	12,689-6	Fluorobenzylamine, 3-	1.0	3.45		125.15	1.097	1		√	634	√		
50	39,165-4	Isopinocampheylamine, (1R,2R,3R,5S)-(-)-	2.0	10.19		153.27	0.909	2		√	662	√		
51	39,166-2	Isopinocampheylamine, (1S,2S,3S,5R)-(+)-	2.0	10.19		153.27	0.909	2		√	662	√		
52	10,906-1	Isopropylamine	2.0	5.15		59.11	0.694	2		√?	568	√		
53	15,988-3	Methoxybenzylamine, 2-	1.0	3.95		137.18	1.051	1		√	646	√		
54	M1,110-3	Methoxybenzylamine, 4-	1.0	3.95		137.18	1.050	1		√	646	√		
55	24,106-7	Methoxyethylamine, 2-	1.0	2.63		75.11	0.864	1		√	584	√		
56	37,359-1	Methoxyphenethylamine, 2-	1.0	4.43		151.21	1.033	1		√	660	√		
57	27,022-9	Methoxyphenethylamine, 3-	1.0	4.40		151.21	1.038	1		√	660	√		
58	18,730-5	Methoxyphenethylamine, 4-	1.0	4.43		151.21	1.033	1		√	660	√		
59	M2,500-7	Methoxypropylamine, 3-	1.0	3.08		89.14	0.874	1		√	598	√		
60	39,505-6	Methylamine (2.0M in THF)	1.0	15.12		500.00	1.000	1		√	540	√		
61	18,080-7	Myrtanylamine, (-)-cis-	1.0	5.06		153.27	0.915	1		√	662	√		
62	12,703-5	Napthylenemethylamine, 1-	1.0	4.43		157.22	1.073	1		√	666	70%		
63	19,166-3	Nitrobenzylamine hydrochloride, 3-	1.1	[illegible]	10.53	188.62	1.000	1	1	60%	662	50%	60%	

Table B. Amine building blocks tested.

Test	Aldrich			mg or uL	uL				acid	√ = ≥90% conversion and purity				FAB rel int
#	Catalog #	Chemical Name	2-pyr	amine	DIPEA	MW	d	mult	salt	HPLC	Mass	LCMS	TLC	Pd/SM
64	18,480-2	Nitrophenethylamine hydrochloride, 4-	1.1	6.13	10.53	202.64	1.000	1	1	NR?	676	10%	10%	
65	O-580-2	Octylamine	1.0	5.00		129.25	0.782	1		√	638	√		
66	40,726-7	Phenethylamine	1.0	3.60		121.18	0.965	1		√	630	√		
±67	P2,237-0	Phenylcyclopropylamine hydrochloride, trans-2-	2.1	10.26	21.06	169.66	1.000	2	1	40%	642	40%	NR?	100/68
±68	P2,555-8	Phenylglycinonitrile hydrochloride, 2-	2.1	10.20	21.06	168.63	1.000	2	1	NR	641	10%	NR?	10/96
69	P4,950-3	Piperonylamine	1.0	3.78		151.17	1.214	1		√	660	√		
70	P5,090-0	Propargyl amine	1.0	2.07		55.08	0.803	1		80%	564	80%		
71	41,293-7	Tetrahydrofurfurylamine, (R)-(-)-	1.0	3.12		101.15	0.980	1		√	610	80%		
72	41,294-5	Tetrahydrofurfurylamine, (S)-(+)-	1.0	3.12		101.15	0.980	1		√	610	√		
73	22,741-2	Tetramethyl-1,3-propanediamine, N,N,2,2-	1.0	4.81		130.24	0.818	1		70%	639	10%	70%	100/-
74	42,327-0	Thiopheneethylamine, 2-	1.0	3.54		127.21	1.087	1		√	636	√		
75	26,904-2	Trifluoroethylamine, 2,2,2-	1.0	2.41		99.06	1.245	1		NR?	608	10%	NR	5/100
76	19,374-7	Tryptamine	1.0	4.84		160.22	1.000	1		70%	669	80%		
77	V130-9	Veratrylamine	1.0	4.56		167.21	1.109	1		NR?	676	80%		
											509			
78	A5,530-6	Aminoethyl)pyridine, 2-(2-	1.0	3.62		122.17	1.021	1		√	631	nuked		
79	A6,540-9	Aminomethyl)pyridine, 3-(	1.0	3.08		108.14	1.062	1		√	617	80%c		
80	29,664-3	Butylamine, (R)-(-)-sec-	2.0	6.05		73.14	0.731	2		√	582	80%p		
81	29,665-1	Butylamine, (S)-(+)-sec-	2.0	6.05		73.14	0.731	2		√	582	80%p		
82	33,650-5	Cyclohexylethylamine, (R)-(-)-1-	2.0	8.99		127.33	0.856	2		√	636	80%p		
83	33,651-3	Cyclohexylethylamine, (S)-(+)-1-	2.0	8.99		127.33	0.856	2		√	636	√		
84	12,681-0	Isoamylamine	1.0	3.51		87.17	0.751	1		√	596	√		
											509			
85	42,193-6	Methylbenzylamine, (R)-(+)-a-	2.0	7.73		121.18	0.940	2		√	630	√		
86	27,745-0	Napthyl)ethylamine, (S)-(-)-1-(1-	2.0	9.7[illegible]		171.25	1.060	2		80%c	680	80%c		
87	34,098-7	Trifluoromethoxy)benzylamine, 4-(	1.0	4.62		191.15	1.252	1		√	700	√		
88	26,349-4	Trifluoromethyl)benzylamine, 3-(	1.0	[illegible]		175.16	1.222	1		√	684	√		

Table C.		Acid building blocks tested.							
		carboxylic acids 58.52 umol (50 eq)							
		amino acid hydrochlorides (italics) neutralized with an additional 50 eq DIPEA							
Test	Aldrich		mg or uL			√ = ≥90% conversion and purity			
#	Catalog #	Chemical Name	acid	MW	d	HPLC	Mass	LCMS	Comment
1	33,882-6	Acetic acid	15.92	57.06	1.049	√	688	√	
2	24,851-7	Acetoxybenzoic acid, 4-	52.71	180.16	1.000	NR/√?	808	20%p	80% OAc
3	23,936-1	Acetylsalicylic acid	52.71	180.16	1.000	√	808	20%p	80% OAc
4	14,723-0	Acrylic acid	20.06	72.06	1.051	50%p	700	50%p	
5	11,771-4	Anisic acid, m-	44.52	152.15	1.000	√	780	80%p	
6	16,997-8	Anisic acid, o-	44.52	152.15	1.000	60%c	780	60%c	
7	11,739-0	Anisic acid, p-	44.52	152.15	1.000	70%p	780	20%p	30%c
8	24,238-1	Benzoic acid	35.73	122.12	1.000	√	750	80%p	
9	30,366-6	Butynoic acid, 2-	24.60	84.07	1.000	70%p	712	40%c	
10	40,324-5	Carboxypropyl)trimethylammonium chloride, (3-	53.15	181.66	1.000	NR?	774	NR	
11	13,269-1	Chloropropionic acid, 3-	31.75	108.52	1.000	20%p	737	10%p	
12	23,956-9	Crotonic acid	25.19	86.09	1.000	√	714	70%p	
13	C8,850-5	Cyanoacetic acid	24.89	85.06	1.000	√	713	10%c	
14	15,716-3	Cyanobenzoic acid, 3-	43.05	147.13	1.000	√	775	80%p	
15	C8,980-3	Cyanobenzoic acid, 4-	43.05	147.13	1.000	√	775	80%p	
16	10,183-4	Cyclohexanecarboxylic acid	36.30	128.17	1.033	√	756	√	
17	C11,200-3	Cyclopentanecarboxylic acid	31.72	114.14	1.053	√	742	√	
18	12,549-0	Cyclopentylacetic acid	36.70	128.17	1.022	√	756	√	
19	C11,660-2	Cyclopropanecarboxylic acid	23.15	86.09	1.088	√	714	80%p	
20	19,572-3	Dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylic acid, 3,4-	49.79	170.16	1.000	60%p	798	60%p	3 isomers
21	30,035-7	Dihydro-2-methylbenzoic acid, 1,4-	40.43	138.17	1.000	√	766	80%p	
22	24,840-9	Dimethylaminobenzoic acid, 3-	48.33	165.19	1.000	40%c?	793	10%c	
23	D13,945-9	Dimethylaminobenzoic acid, 4-	48.33	165.19	1.000	NR	793	NR	
24	29,223-0	Dimethylglycine, N,N-	30.17	103.12	1.000	NR?	731	10%c	
25	33,504-5	Ferroceneacetic acid	71.42	244.08	1.000	70%c	872	70%c	
26	25,136-4	Formic acid	11.04	46.03	1.220	NR/√?	674	NR	
27	33,638-6	Furanacrylic acid, trans-3-	40.41	138.12	1.000	√	766	√	
28	F2,050-5	Furoic acid, 2-	32.79	112.08	1.000	√	740	√	

Table C.		Acid building blocks tested.								
Test	Aldrich		mg or uL			√ = ≥90% conversion and purity				
#	Catalog #	Chemical Name	acid	MW	d	HPLC	Mass	LCMS	Comment
29	16,339-2	Furoic acid, 3-	32.79	112.08	1.000	√	740	√	
30	F2,080-7	Furylacrylic acid	40.41	138.12	1.000	40%p	766	10%p	798?
31	24,010-9	Hexadienoic acid, 2,4- (Sorbic acid)	32.81	112.13	1.000	√	740	√	
32	24,016-8	Isobutyric acid	27.14	88.11	0.950	√	716	√	
33	I-1,750-8	Isonicotinic acid	36.02	123.11	1.000	√	751	√	
34	12,954-2	Isovaleric acid	31.89	102.13	0.937	√	730	√	
35	L200-9	Levulinic acid	29.96	116.12	1.134	80%p	744	80%p	
36	85,601-0	Linolenic acid	89.14	278.44	0.914	√	906	938?	FAB: 906 √
37'	44,869-7	Menthoxyacetic acid, (+)-	61.48	214.31	1.020	√	842	√	
38	M300-0	Menthoxyacetic acid, (-)-	61.48	214.31	1.020	√	842	√	
39	39,537-4	Methacrylic acid	24.82	86.09	1.015	70%p	714	70%p	
40	19,455-7	Methoxyacetic acid	22.45	90.08	1.174	√	718	√	
41	24,896-7	Methoxyphenylacetic acid, (R)-(-)-a-	48.62	166.18	1.000	70%p	794	60%p	40% diast
42	24,898-3	Methoxyphenylacetic acid, (S)-(+)-a-	48.62	166.18	1.000	60%p	794	60%p	40% diast
43	18,065-3	Methoxyphenylacetic acid, 2-	48.62	166.18	1.000	√	794	√	
44	M1,900-7	Methoxyphenylacetic acid, 3-	48.62	166.18	1.000	80%c	794	80%c	
45	M1,920-1	Methoxyphenylacetic acid, 4-	48.62	166.18	1.000	√	794	√	
46	36,728-1	Methyl (1S,2R)-(+)-cis-1,2,3,6-tetrahydrophthalate, 1-	53.89	184.19	1.000	√	812	√	
47	M4,735-3	Methyl glutarate, mono-	37.54	146.14	1.139	√	774	√	
48	31,764-0	Methyl phthalate, mono-	52.71	180.16	1.000	√	808	√	
49	32,838-3	Methyl terephthalate, mono-	52.71	180.16	1.000	√	808	√	
50	29,295-8	Methyl-2-(nitromethyl)-5-oxocyclopentaneacetic acid,	62.97	215.21	1.000	NR	843	NR	
		[1R-(1-a,2b,3a)]-(+)-3-							
51	19,755-6	Methyl-5-oxo-2-pyrazolin-1-yl)benzoic acid, 4-(3-	63.85	218.21	1.000	NR?	846	NR	
52	41,749-1	Methylchromone-2-carboxylic acid, 6-	59.75	204.19	1.000	10%p	832	30%p	
53	32,967-3	Methylenedioxy)phenylacetic acid, 3,4-(	52.71	180.16	1.000	80%c	808	√	
54	13,415-5	Methylindole-2-carboxylic acid, 1-	51.25	175.19	1.000	√	803	√	
55	N765-0	Nicotinic acid	36.02	123.11	1.000	√	751	√	
56	15,571-3	Nitro-2-furoic acid, 5-	45.96	157.08	1.000	50%p	785	10%p	80% 754?

Table C.	Acid building blocks tested.								
						√ = ≥90% conversion and purity			
Test #	Aldrich Catalog #	Chemical Name	mg or uL acid	MW	d	HPLC	Mass	LCMS	Comment
57	N1,179-5	Nitrobenzoic acid, 4-	48.90	167.12	1.000	60%p	795	60%p	809?
58	N2,020-4	Nitrophenylacetic acid, 4-	53.00	181.15	1.000	NR/√?	809	NR	
59	N2,290-8	Nitropropionic acid, 3-	34.84	119.08	1.000	NR	747	NR	
60	12,726-4	Norbornaneacetic acid, 2-	42.37	154.21	1.065	√	782	√	
61	O-840-2	Orotic acid monohydrate	50.94	174.11	1.000	NR/√?	784	NR	
62	39,134-4	Oxo-4-phenyl-3-oxazolidineacetic acid, (S)-(+)-2-	64.73	221.21	1.000	√	849	√	
63	32,285-7	Oxotricyclo[2.2.1.0(2,6)]heptane-7-carboxylic acid, anti-3-	44.52	152.15	1.000	√	780	√	
64	P1,662-1	Phenylacetic acid	36.86	136.15	1.081	60%c	764	90%c	
65	P3,120-5	Phenylpropiolic acid	42.76	146.15	1.000	60%c?	774	10%c	
66	21,183-4	Phthalylsulfathiazole	118.05	403.44	1.000	NR	1031	NR	
67	P4,280-0	Picolinic acid	36.02	123.11	1.000	√	751	√	
68	40,290-7	Propionic acid	21.83	74.08	0.993	√	702	√	
69	P5,610-0	Pyrazinecarboxylic acid, 2-	36.31	124.10	1.000	√	752	√	
70	*P6,560-6*	*Pyridylacetic acid hydrochloride, 2-*	*50.80*	*173.60*	*1.000*	NR	766	NR	
71	*P6,580-0*	*Pyridylacetic acid hydrochloride, 3-*	*50.80*	*173.60*	*1.000*	NR?	766	NR	
72	*P6,585-1*	*Pyridylacetic acid hydrochloride, 4-*	*50.80*	*173.60*	*1.000*	NR?	766	NR	
73	27,553-0	Pyrimidylthio)acetic acid, (2-	49.80	170.19	1.000	NR/√?	798	NR	
74	10,736-0	Pyruvic acid	20.34	88.06	1.267	NR/√?	716	NR	
±75	34,151-7	Tetrahydro-2-furoic acid	28.10	116.12	1.209	60%p	744	60/40	2 diast
±76	33,995-4	Tetrahydro-3-furoic acid	27.99	116.12	1.214	√	744	√	2 diast
77	T2,860-6	Thioctic acid	60.37	206.33	1.000	nuked	834	0%p	60% 866?
78	19,594-4	Thiopheneacetic acid, 2-	41.60	142.18	1.000	NR?	770	NR	
79	22,063-9	Thiopheneacetic acid, 3-	41.60	142.18	1.000	50%c	770	50%c	
80	T3,260-3	Thiophenecarboxylic acid, 2-	37.50	128.15	1.000	√	756	√	
81	24,776-6	Thiophenecarboxylic acid, 3-	37.50	128.15	1.000	√	756	√	
82	22,227-5	Thiopheneglyoxylic acid, 2-	45.69	156.16	1.000	NR	784	NR	
83'	23,302-1	Trifluoro-p-tolyl)acetic acid, (a,a,a-	53.73	204.15	1.000	NR	832	20%c	
84	13,471-6	Vinylacetic acid	21.87	86.09	1.013	√	714	√	

Table C.		Acid building blocks tested.							
Questionable starting material quality for 85-98									
Test	Aldrich		mg or ul			√ = ≥90% conversion and purity			
#	Catalog #	Chemical Name	acid	MW	d	HPLC	Mass	LCMS	Comment
85	30,234-1	Acetoxyacetic acid	34.55	118.09	1.000	70%p	746	40%p	
86	30,727-0	Benzofurancarboxylic acid, 2-	47.44	162.14	1.000	30%p	790	60%p	OK
87	C8,215-9	Cinnoline-4-carboyxlic acid	50.96	174.16	1.000	30%p	802	60%p	OK
88	D12,380-3	Diiodo-4-pyridone-1-acetic acid, 3,5-	118.48	404.93	1.000	10%p	1033	NR	
89	D13,860-6	Dimethylacrylic acid, 3,3-	29.30	100.12	1.000	10%p	728	50%c	
90	10,668-7	Ferrocenecarboxylic acid	67.31	230.05	1.000	20%p	858	NR	
91	22,526-2	Methoxy-1-indanone-3-acetic acid, 6-	64.44	220.23	1.000	30%p	848	50%p	OK
92	15,314-1	Methyl-2-pyrrolecarboxylic acid, 1-	36.61	125.13	1.000	20%p	753	NR	
93	41,077-2	Oxo-1-indancarboxylic acid, 3-	51.55	176.17	1.000	40%c	804	NR	
94	P6,620-3	Pyridyl)acrylic acid, trans-3-(3-	43.64	149.15	1.000	√/NR?	777	80%p	OK
95	13,058-3	Thienyl)acrylic acid, 3-(2-	45.12	154.19	1.000	40%p	782	60%p	OK
96	18,834-4	Trifluoro-m-toluic acid, a,a,a-	55.63	190.12	1.000	40%p	818	70%p	OK
97	19,688-6	Trifluoro-o-toluic acid,. a,a,a-	55.63	190.12	1.000	40%p	818	60%p	OK
98	19,689-4	Trifluoro-p-toluic acid, a,a,a-	55.63	190.12	1.000	40%p	818	60%p	OK

Table D.		Alkyne building blocks used in test library synthesis.									
		mono terminal alkyne	153.65	umol alkyne (20 eq)							
	Test		mg or uL							LCMS	Rel
BB#	#	Chemical Name	alkyne	MW	d	Vendor	Catalog #	HPLC	Mass	Int	Int
1	25	Methyl-1-buten-3-yne, 2-	[redacted]	66.10	0.695	Aldrich	M3,280-1	√	380	0.0047	0.12
2	24	Methyl propargyl ether	[redacted]	70.09	0.830	Aldrich	17,719-9	80%c	384	0.0020	0.05
3	11	Dimethyl-1-butyne, 3,3-	[redacted]	82.15	0.667	Aldrich	24,439-2	√	396	0.0433	1.12
4	23	Hexynenitrile, 5-	[redacted]	93.13	0.889	Aldrich	27,134-9	√	407	0.0092	0.24
5	31	Phenylacetylene	[redacted]	102.14	0.930	Aldrich	11,770-6	√	416	0.0271	0.70
6	30	Phenyl-1-propyne, 3-	[redacted]	116.16	0.934	Aldrich	37,684-1	√	430	0.0297	0.77
7	-	SKIP CODON	[redacted]	128.00	1.000	-	-	√	442	0.1160	2.99
8	8	Decadiyne, 1,5-	[redacted]	134.22	1.000	GFS	126706	√	448	0.0788	2.03
			AVERAGE	*99.00*					*413*	*0.0388*	

Table E.		Amine building blocks used in test library synthesis.									
		beta-branched or greater (mult.= 1)	185.70	umol amine (25 eq)							
		alpha-branched (mult = 2)	371.40	umol amine (50 eq)							
		2-hydroxypyridine (2-pyr)	1.0	37.14							
		stock solutions	2.0	74.28							
	Test			mg or ul				Aldrich		LCMS	Rel
BB#	#	Chemical Name	2-pyr	amine	MW	d	mult	Catalog #	Mass	Int	Int
1	-	SKIP CODON	-	-	0.00	-	-	-	380	0.032	0.57
									384	0.016	0.28
									396	0.114	2.07
									407	0.056	1.02
									416	0.052	0.94
									430	0.055	1.01
									442	0.046	0.83
									448	0.074	1.34
								AVERAGE	413	0.055	
2	60	Methylamine (2.0M in THF)	1.0	92.85	500.00	1.000	1	39,505-6	411	0.056	0.39
									415	0.080	0.55
									427	0.209	1.45
									438	0.103	0.72
									447	0.140	0.97
									461	0.182	1.26
									473	0.057	0.39
									479	0.328	2.28
								AVERAGE	444	0.144	
3	55	Methoxyethylamine, 2-	1.0	15.19	75.11	0.864	1	24,106-7	455	0.109	0.48
									459	0.142	0.62
									471	0.410	1.79
									482	0.162	0.71
									491	0.266	1.16
									505	0.270	1.18
									517	0.088	0.38
									523	0.385	1.68
								AVERAGE	488	0.229	
4	35	Cyclopentylamine	2.0	36.65	85.15	0.863	2	C11,500-2	465	0.080	0.50
									469	0.116	0.73
									481	0.319	1.99
									492	0.179	1.12
									501	0.173	1.08
									515	0.108	0.68
									527	0.109	0.68
									533	0.194	1.21
								AVERAGE	498	0.160	
5	33	Cyclohexanemethylamine	1.0	24.16	113.20	0.870	1	10,184-2	493	0.389	0.76
									497	0.455	0.89
									509	0.819	1.59
									520	0.401	0.78
									529	0.553	1.08
									543	0.614	1.19
									555	0.303	0.59
									561	0.578	1.12
								AVERAGE	526	0.514	

Table E.	Amine building blocks used in test library synthesis.										
	Test			mg or ul				Aldrich		LCMS	Rel
BB#	#	Chemical Name	2-pyr	amine	MW	d	mult	Catalog #	Mass	Int	Int
6	22	Aminopropyl)-2-pyrrolidinone, 1-(3-	1.0	26.03	142.20	1.014	1	13,656-5	522	0.009	0.64
									526	0.013	0.91
									538	0.022	1.57
									549	0.012	0.84
									558	0.010	0.71
									572	0.010	0.71
									584	0.005	0.35
									590	0.029	2.10
								AVERAGE	*555*	*0.014*	
7	62	Napthylenemethylamine, 1-	1.0	27.21	157.22	1.073	1	12,703-5	537	0.144	0.45
									541	0.324	1.02
									553	0.524	1.65
									564	0.369	1.16
									573	0.247	0.78
									587	0.279	0.88
									599	0.287	0.91
									605	0.365	1.15
								AVERAGE	*570*	*0.317*	
8	77	Veratrylamine	1.0	28.00	167.21	1.109	1	V130-9	547	0.168	0.66
									551	0.136	0.53
									563	0.532	2.08
									574	0.227	0.89
									583	0.229	0.89
									597	0.266	1.04
									609	0.184	0.72
									615	0.303	1.18
								AVERAGE	*580*	*0.256*	
				AVERAGE	*155.01*						

Table F.		Acid building blocks used in test library synthesis.										
		carboxylic acids 326.5 umol (50 eq)										
Expected Mass Coding Scheme: (Acid, Alkyne, Amine) followed by mass calculations												
Butyrolactone (aminolysis skip codon) compounds are common to each pool (italicized)												
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
1	-	SKIP CODON		-	-							
(1, 1, 1)		*442.0+-18.0+18.0+-128.0+66.0+0.0+0.0=*				*380*	*5.62*	*0.054*	*0.21*			
(1, 1, 2)		442.0+-18.0+18.0+-128.0+66.0+0.0+31.0=				411	4.24	0.109	0.43			
(1, 1, 3)		442.0+-18.0+18.0+-128.0+66.0+0.0+75.0=				455	4.58	0.266	1.06			
(1, 1, 4)		442.0+-18.0+18.0+-128.0+66.0+0.0+85.0=				465	5.60	0.191	0.76			
(1, 1, 5)		442.0+-18.0+18.0+-128.0+66.0+0.0+113.0=				493	6.45	0.270	1.07			
(1, 1, 6)		442.0+-18.0+18.0+-128.0+66.0+0.0+142.0=				522	5.49	0.067	0.26			
(1, 1, 7)		442.0+-18.0+18.0+-128.0+66.0+0.0+157.0=				537	6.40	0.270	1.07			
(1, 1, 8)		442.0+-18.0+18.0+-128.0+66.0+0.0+167.0=				547	5.33	0.182	0.72			
(1, 2, 1)		*442.0+-18.0+18.0+-128.0+70.0+0.0+0.0=*				*384*	*3.97*	*0.031*	*0.12*		*1*	
(1, 2, 2)		442.0+-18.0+18.0+-128.0+70.0+0.0+31.0=				415	1.62	0.122	0.48			
(1, 2, 3)		442.0+-18.0+18.0+-128.0+70.0+0.0+75.0=				459	1.92	0.262	1.04			
(1, 2, 4)		442.0+-18.0+18.0+-128.0+70.0+0.0+85.0=				469	4.10	0.241	0.96			
(1, 2, 5)		442.0+-18.0+18.0+-128.0+70.0+0.0+113.0=				497	5.36	0.414	1.64			
(1, 2, 6)		442.0+-18.0+18.0+-128.0+70.0+0.0+142.0=				526	1.44	0.018	0.07	1	1	
(1, 2, 7)		442.0+-18.0+18.0+-128.0+70.0+0.0+157.0=				541	5.44	0.344	1.37			
(1, 2, 8)		442.0+-18.0+18.0+-128.0+70.0+0.0+167.0=				551	3.86	0.219	0.87			
(1, 3, 1)		*442.0+-18.0+18.0+-128.0+82.0+0.0+0.0=*				*396*	*6.05*	*0.121*	*0.48*			
(1, 3, 2)		442.0+-18.0+18.0+-128.0+82.0+0.0+31.0=				427	4.90	0.307	1.22			
(1, 3, 3)		442.0+-18.0+18.0+-128.0+82.0+0.0+75.0=				471	5.17	0.647	2.57			
(1, 3, 4)		442.0+-18.0+18.0+-128.0+82.0+0.0+85.0=				481	6.10	0.422	1.67			
(1, 3, 5)		442.0+-18.0+18.0+-128.0+82.0+0.0+113.0=				509	6.99	0.565	2.24			
(1, 3, 6)		442.0+-18.0+18.0+-128.0+82.0+0.0+142.0=				538	4.56	0.050	0.20			
(1, 3, 7)		442.0+-18.0+18.0+-128.0+82.0+0.0+157.0=				553	6.88	0.410	1.63			
(1, 3, 8)		442.0+-18.0+18.0+-128.0+82.0+0.0+167.0=				563	5.78	0.438	1.74			
(1, 4, 1)		*442.0+-18.0+18.0+-128.0+93.0+0.0+0.0=*				*407*	*4.50*	*0.146*	*0.58*			
(1, 4, 2)		442.0+-18.0+18.0+-128.0+93.0+0.0+31.0=				438	2.02	0.190	0.75			
(1, 4, 3)		442.0+-18.0+18.0+-128.0+93.0+0.0+75.0=				482	2.50	0.253	1.00			
(1, 4, 4)		442.0+-18.0+18.0+-128.0+93.0+0.0+85.0=				492	4.53	0.283	1.12			
(1, 4, 5)		442.0+-18.0+18.0+-128.0+93.0+0.0+113.0=				520	5.49	0.532	2.11			
(1, 4, 6)		442.0+-18.0+18.0+-128.0+93.0+0.0+142.0=				549	1.76	0.010	0.04	1	1	
(1, 4, 7)		442.0+-18.0+18.0+-128.0+93.0+0.0+157.0=				564	5.57	0.377	1.50			
(1, 4, 8)		442.0+-18.0+18.0+-128.0+93.0+0.0+167.0=				574	4.37	0.291	1.15			
(1, 5, 1)		*442.0+-18.0+18.0+-128.0+102.0+0.0+0.0=*				*416*	*5.97*	*0.086*	*0.34*			
(1, 5, 2)		442.0+-18.0+18.0+-128.0+102.0+0.0+31.0=				447	4.93	0.201	0.80			
(1, 5, 3)		442.0+-18.0+18.0+-128.0+102.0+0.0+75.0=				491	5.14	0.483	1.92			
(1, 5, 4)		442.0+-18.0+18.0+-128.0+102.0+0.0+85.0=				501	6.00	0.303	1.20			
(1, 5, 5)		442.0+-18.0+18.0+-128.0+102.0+0.0+113.0=				529	6.77	0.385	1.53			
(1, 5, 6)		442.0+-18.0+18.0+-128.0+102.0+0.0+142.0=				558	4.61	0.020	0.08	1	1	
(1, 5, 7)		442.0+-18.0+18.0+-128.0+102.0+0.0+157.0=				573	6.69	0.315	1.25			
(1, 5, 8)		442.0+-18.0+18.0+-128.0+102.0+0.0+167.0=				583	5.70	0.291	1.15			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
.1	-	SKIP CODON	[redacted]	-	-							
(1, 6, 1)		*442.0+-18.0+18.0+-128.0+116.0+0.0+0.0=*				*430*	*6.05*	*0.081*	*0.32*			
(1, 6, 2)		442.0+-18.0+18.0+-128.0+116.0+0.0+31.0=				461	5.06	0.242	0.96			
(1, 6, 3)		442.0+-18.0+18.0+-128.0+116.0+0.0+75.0=				505	5.28	0.516	2.05			
(1, 6, 4)		442.0+-18.0+18.0+-128.0+116.0+0.0+85.0=				515	6.05	0.279	1.11			
(1, 6, 5)		442.0+-18.0+18.0+-128.0+116.0+0.0+113.0=				543	6.85	0.324	1.29			
(1, 6, 6)		442.0+-18.0+18.0+-128.0+116.0+0.0+142.0=				572	4.96	0.009	0.04	1	1	
(1, 6, 7)		442.0+-18.0+18.0+-128.0+116.0+0.0+157.0=				587	6.72	0.311	1.23			
(1, 6, 8)		442.0+-18.0+18.0+-128.0+116.0+0.0+167.0=				597	5.78	0.266	1.06			
(1, 7, 1)		*442.0+-18.0+18.0+-128.0+128.0+0.0+0.0=*				*442*	*4.64*	*0.114*	*0.45*			
(1, 7, 2)		442.0+-18.0+18.0+-128.0+128.0+0.0+31.0=				473	1.97	0.093	0.37			
(1, 7, 3)		442.0+-18.0+18.0+-128.0+128.0+0.0+75.0=				517	2.56	0.291	1.15			
(1, 7, 4)		442.0+-18.0+18.0+-128.0+128.0+0.0+85.0=				527	4.77	0.234	0.93			
(1, 7, 5)		442.0+-18.0+18.0+-128.0+128.0+0.0+113.0=				555	5.84	0.365	1.45			
(1, 7, 6)		442.0+-18.0+18.0+-128.0+128.0+0.0+142.0=				584	5.70	0.120	0.48			
(1, 7, 7)		442.0+-18.0+18.0+-128.0+128.0+0.0+157.0=				599	5.84	0.307	1.22			
(1, 7, 8)		442.0+-18.0+18.0+-128.0+128.0+0.0+167.0=				609	4.45	0.236	0.94			
(1, 8, 1)		*442.0+-18.0+18.0+-128.0+134.0+0.0+0.0=*				*448*	*6.80*	*0.095*	*0.38*			
(1, 8, 2)		442.0+-18.0+18.0+-128.0+134.0+0.0+31.0=				479	5.92	0.311	1.23			
(1, 8, 3)		442.0+-18.0+18.0+-128.0+134.0+0.0+75.0=				523	6.10	0.483	1.92			
(1, 8, 4)		442.0+-18.0+18.0+-128.0+134.0+0.0+85.0=				533	6.90	0.254	1.01			
(1, 8, 5)		442.0+-18.0+18.0+-128.0+134.0+0.0+113.0=				561	7.68	0.377	1.50			
(1, 8, 6)		442.0+-18.0+18.0+-128.0+134.0+0.0+142.0=				590	5.62	0.028	0.11		1	
(1, 8, 7)		442.0+-18.0+18.0+-128.0+134.0+0.0+157.0=				605	7.52	0.299	1.19			
(1, 8, 8)		442.0+-18.0+18.0+-128.0+134.0+0.0+167.0=				615	6.53	0.319	1.27			
					AVERAGE	*509*	*5.2*	*0.252*	*TOTAL*	*4*	*6*	
2	1	Acetic acid	[illegible]	57.06	1.049							
(2, 1, 1)						*380*	*5.57*	*0.029*	*0.05*	*1*	*1*	
(2, 1, 2)		442.0+-18.0+60.0+-128.0+66.0+0.0+31.0=				453	4.90	0.348	0.66			
(2, 1, 3)		442.0+-18.0+60.0+-128.0+66.0+0.0+75.0=				497	5.22	0.782	1.47			
(2, 1, 4)		442.0+-18.0+60.0+-128.0+66.0+0.0+85.0=				507	5.94	0.315	0.59			
(2, 1, 5)		442.0+-18.0+60.0+-128.0+66.0+0.0+113.0=				535	6.66	0.610	1.15			
(2, 1, 6)		442.0+-18.0+60.0+-128.0+66.0+0.0+142.0=				564	4.56	0.020	0.04	1	1	
(2, 1, 7)		442.0+-18.0+60.0+-128.0+66.0+0.0+157.0=				579	6.64	0.397	0.75			
(2, 1, 8)		442.0+-18.0+60.0+-128.0+66.0+0.0+167.0=				589	5.57	0.365	0.69			
(2, 2, 1)						*384*	*4.21*	*0.046*	*0.09*	*1*	*1*	
(2, 2, 2)		442.0+-18.0+60.0+-128.0+70.0+0.0+31.0=				457	2.31	0.299	0.56			
(2, 2, 3)		442.0+-18.0+60.0+-128.0+70.0+0.0+75.0=				501	3.10	0.389	0.73			
(2, 2, 4)		442.0+-18.0+60.0+-128.0+70.0+0.0+85.0=				511	4.80	0.795	1.50			
(2, 2, 5)		442.0+-18.0+60.0+-128.0+70.0+0.0+113.0=				539	5.38	0.692	1.30			
(2, 2, 6)		442.0+-18.0+60.0+-128.0+70.0+0.0+142.0=				568	1.89	0.038	0.07	1	1	
(2, 2, 7)		442.0+-18.0+60.0+-128.0+70.0+0.0+157.0=				583	5.76	0.406	0.76			
(2, 2, 8)		442.0+-18.0+60.0+-128.0+70.0+0.0+167.0=				593	4.42	0.541	1.02			
(2, 3, 1)						*396*	*6.98*	*0.080*	*0.15*		*1*	
(2, 3, 2)		442.0+-18.0+60.0+-128.0+82.0+0.0+31.0=				489	5.38	1.100	2.07			
(2, 3, 3)		442.0+-18.0+60.0+-128.0+82.0+0.0+75.0=				513	5.70	0.831	1.56			
(2, 3, 4)		442.0+-18.0+60.0+-128.0+82.0+0.0+85.0=				523	6.42	1.050	1.98			
(2, 3, 5)		442.0+-18.0+60.0+-128.0+82.0+0.0+113.0=				551	7.17	1.230	2.32			
(2, 3, 6)		442.0+-18.0+60.0+-128.0+82.0+0.0+142.0=				580	5.09	0.900	1.69			
(2, 3, 7)		442.0+-18.0+60.0+-128.0+82.0+0.0+157.0=				595	7.06	1.100	2.07			
(2, 3, 8)		442.0+-18.0+60.0+-128.0+82.0+0.0+167.0=				605	5.97	0.688	1.30			

Table F.	Acid building blocks used in test library synthesis.											
BB#	Test #	Chemical Name	mg or uL acid	MW	d	Mass	Ret Time	LCMS Intensity	Rel Int	< 10% Rel Int	< 20% Rel Int	Mult Peaks
2	1	Acetic acid	[illegible]	57.06	1.049							
(2, 4, 1)						*407*	*4.50*	*0.116*	*0.22*			
(2, 4, 2)		442.0+-18.0+60.0+-128.0+93.0+0.0+31.0=				480	3.09	0.340	0.64			
(2, 4, 3)		442.0+-18.0+60.0+-128.0+93.0+0.0+75.0=				524	3.97	0.594	1.12			
(2, 4, 4)		442.0+-18.0+60.0+-128.0+93.0+0.0+85.0=				534	5.01	0.807	1.52			
(2, 4, 5)		442.0+-18.0+60.0+-128.0+93.0+0.0+113.0=				562	5.73	0.725	1.37			
(2, 4, 6)		442.0+-18.0+60.0+-128.0+93.0+0.0+142.0=				591	2.50	0.020	0.04	1	1	
(2, 4, 7)		442.0+-18.0+60.0+-128.0+93.0+0.0+157.0=				606	5.81	0.692	1.30			
(2, 4, 8)		442.0+-18.0+60.0+-128.0+93.0+0.0+167.0=				616	4.72	0.643	1.21			
(2, 5, 1)						*416*	*6.02*	*0.048*	*0.09*	*1*	*1*	
(2, 5, 2)		442.0+-18.0+60.0+-128.0+102.0+0.0+31.0=				489	5.36	0.590	1.11			
(2, 5, 3)		442.0+-18.0+60.0+-128.0+102.0+0.0+75.0=				533	5.62	0.815	1.53			
(2, 5, 4)		442.0+-18.0+60.0+-128.0+102.0+0.0+85.0=				543	6.29	0.557	1.05			
(2, 5, 5)		442.0+-18.0+60.0+-128.0+102.0+0.0+113.0=				571	6.96	0.582	1.10			
(2, 5, 6)		442.0+-18.0+60.0+-128.0+102.0+0.0+142.0=				600	5.04	0.042	0.08	1	1	
(2, 5, 7)		442.0+-18.0+60.0+-128.0+102.0+0.0+157.0=				615	6.90	0.639	1.20			
(2, 5, 8)		442.0+-18.0+60.0+-128.0+102.0+0.0+167.0=				625	5.92	0.557	1.05			
(2, 6, 1)						*430*	*6.05*	*0.078*	*0.15*		*1*	
(2, 6, 2)		442.0+-18.0+60.0+-128.0+116.0+0.0+31.0=				503	5.46	0.569	1.07			
(2, 6, 3)		442.0+-18.0+60.0+-128.0+116.0+0.0+75.0=				547	5.70	0.492	0.93			
(2, 6, 4)		442.0+-18.0+60.0+-128.0+116.0+0.0+85.0=				557	6.34	0.569	1.07			
(2, 6, 5)		442.0+-18.0+60.0+-128.0+116.0+0.0+113.0=				585	6.98	0.737	1.39			
(2, 6, 6)		442.0+-18.0+60.0+-128.0+116.0+0.0+142.0=				614	5.17	0.041	0.08	1	1	
(2, 6, 7)		442.0+-18.0+60.0+-128.0+116.0+0.0+157.0=				629	6.93	0.643	1.21			
(2, 6, 8)		442.0+-18.0+60.0+-128.0+116.0+0.0+167.0=				639	5.97	0.504	0.95			
(2, 7, 1)						*442*	*4.66*	*0.096*	*0.18*		*1*	
(2, 7, 2)		442.0+-18.0+60.0+-128.0+128.0+0.0+31.0=				515	3.25	0.208	0.39			
(2, 7, 3)		442.0+-18.0+60.0+-128.0+128.0+0.0+75.0=				559	4.21	0.688	1.30			
(2, 7, 4)		442.0+-18.0+60.0+-128.0+128.0+0.0+85.0=				569	5.30	0.606	1.14			
(2, 7, 5)		442.0+-18.0+60.0+-128.0+128.0+0.0+113.0=				597	6.13	0.795	1.50			
(2, 7, 6)		442.0+-18.0+60.0+-128.0+128.0+0.0+142.0=				626	5.92	0.251	0.47			
(2, 7, 7)		442.0+-18.0+60.0+-128.0+128.0+0.0+157.0=				641	6.16	0.766	1.44			
(2, 7, 8)		442.0+-18.0+60.0+-128.0+128.0+0.0+167.0=				651	4.85	0.418	0.79			
(2, 8, 1)						*448*	*6.82*	*0.108*	*0.20*			
(2, 8, 2)		442.0+-18.0+60.0+-128.0+134.0+0.0+31.0=				521	6.26	0.938	1.77			
(2, 8, 3)		442.0+-18.0+60.0+-128.0+134.0+0.0+75.0=				565	6.50	1.080	2.03			
(2, 8, 4)		442.0+-18.0+60.0+-128.0+134.0+0.0+85.0=				575	7.17	0.493	0.93			
(2, 8, 5)		442.0+-18.0+60.0+-128.0+134.0+0.0+113.0=				603	7.81	1.060	2.00			
(2, 8, 6)		442.0+-18.0+60.0+-128.0+134.0+0.0+142.0=				632	5.97	0.046	0.09	1	1	
(2, 8, 7)		442.0+-18.0+60.0+-128.0+134.0+0.0+157.0=				647	7.68	1.230	2.32			
(2, 8, 8)		442.0+-18.0+60.0+-128.0+134.0+0.0+167.0=				657	6.69	0.766	1.44			
					AVERAGE	*546*	*5.5*	*0.531*	*TOTAL*	*9*	*12*	
3	40	Methoxyacetic acid	[illegible]25.05	90.08	1.174							
(3, 1, 1)						*380*	*5.57*	*0.025*	*0.04*	*1*	*1*	
(3, 1, 2)		442.0+-18.0+90.0+-128.0+66.0+0.0+31.0=				483	4.90	0.524	0.84			
(3, 1, 3)		442.0+-18.0+90.0+-128.0+66.0+0.0+75.0=				527	5.22	0.856	1.37			
(3, 1, 4)		442.0+-18.0+90.0+-128.0+66.0+0.0+85.0=				537	5.97	0.360	0.58			
(3, 1, 5)		442.0+-18.0+90.0+-128.0+66.0+0.0+113.0=				565	6.66	0.561	0.90			
(3, 1, 6)		442.0+-18.0+90.0+-128.0+66.0+0.0+142.0=				594	4.64	0.030	0.05	1	1	
(3, 1, 7)		442.0+-18.0+90.0+-128.0+66.0+0.0+157.0=				609	6.61	0.582	0.93			
(3, 1, 8)		442.0+-18.0+90.0+-128.0+66.0+0.0+167.0=				619	5.57	0.561	0.90			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
3	40	Methoxyacetic acid	25.05	90.08	1.174							
(3, 2, 1)						*384*	*4.24*	*0.047*	*0.07*	*1*	*1*	
(3, 2, 2)		442.0+-18.0+90.0+-128.0+70.0+0.0+31.0=				487	2.32	0.340	0.54			
(3, 2, 3)		442.0+-18.0+90.0+-128.0+70.0+0.0+75.0=				531	3.22	0.442	0.71			
(3, 2, 4)		442.0+-18.0+90.0+-128.0+70.0+0.0+85.0=				541	4.80	0.635	1.01			
(3, 2, 5)		442.0+-18.0+90.0+-128.0+70.0+0.0+113.0=				569	5.65	0.725	1.16			
(3, 2, 6)		442.0+-18.0+90.0+-128.0+70.0+0.0+142.0=				598	1.97	0.042	0.07	1	1	
(3, 2, 7)		442.0+-18.0+90.0+-128.0+70.0+0.0+157.0=				613	5.73	0.586	0.94			
(3, 2, 8)		442.0+-18.0+90.0+-128.0+70.0+0.0+167.0=				623	4.45	0.713	1.14			
(3, 3, 1)						*396*	*6.98*	*0.082*	*0.13*		*1*	*3*
(3, 3, 2)		442.0+-18.0+90.0+-128.0+82.0+0.0+31.0=				499	5.41	1.570	2.51			
(3, 3, 3)		442.0+-18.0+90.0+-128.0+82.0+0.0+75.0=				543	5.70	1.050	1.68			
(3, 3, 4)		442.0+-18.0+90.0+-128.0+82.0+0.0+85.0=				553	6.42	1.310	2.09			
(3, 3, 5)		442.0+-18.0+90.0+-128.0+82.0+0.0+113.0=				581	7.17	1.510	2.41			
(3, 3, 6)		442.0+-18.0+90.0+-128.0+82.0+0.0+142.0=				610	5.14	0.100	0.16		1	
(3, 3, 7)		442.0+-18.0+90.0+-128.0+82.0+0.0+157.0=				625	7.06	1.440	2.30			
(3, 3, 8)		442.0+-18.0+90.0+-128.0+82.0+0.0+167.0=				635	6.00	1.080	1.73			
(3, 4, 1)						*407*	*4.53*	*0.115*	*0.18*		*1*	
(3, 4, 2)		442.0+-18.0+90.0+-128.0+93.0+0.0+31.0=				510	3.20	0.307	0.49			
(3, 4, 3)		442.0+-18.0+90.0+-128.0+93.0+0.0+75.0=				554	3.97	0.717	1.15			
(3, 4, 4)		442.0+-18.0+90.0+-128.0+93.0+0.0+85.0=				564	5.01	0.668	1.07			
(3, 4, 5)		442.0+-18.0+90.0+-128.0+93.0+0.0+113.0=				592	5.76	0.684	1.09			
(3, 4, 6)		442.0+-18.0+90.0+-128.0+93.0+0.0+142.0=				621	2.50	0.030	0.05	1	1	
(3, 4, 7)		442.0+-18.0+90.0+-128.0+93.0+0.0+157.0=				636	5.78	0.840	1.34			
(3, 4, 8)		442.0+-18.0+90.0+-128.0+93.0+0.0+167.0=				646	4.72	0.864	1.38			
(3, 5, 1)						*416*	*6.00*	*0.034*	*0.05*	*1*	*1*	
(3, 5, 2)		442.0+-18.0+90.0+-128.0+102.0+0.0+31.0=				519	5.38	0.709	1.13			
(3, 5, 3)		442.0+-18.0+90.0+-128.0+102.0+0.0+75.0=				563	5.62	0.897	1.43			
(3, 5, 4)		442.0+-18.0+90.0+-128.0+102.0+0.0+85.0=				573	6.29	0.676	1.08			
(3, 5, 5)		442.0+-18.0+90.0+-128.0+102.0+0.0+113.0=				601	6.93	0.848	1.35			
(3, 5, 6)		442.0+-18.0+90.0+-128.0+102.0+0.0+142.0=				630	5.12	0.058	0.09	1	1	
(3, 5, 7)		442.0+-18.0+90.0+-128.0+102.0+0.0+157.0=				645	6.90	0.844	1.35			
(3, 5, 8)		442.0+-18.0+90.0+-128.0+102.0+0.0+167.0=				655	5.89	0.860	1.37			
(3, 6, 1)						*430*	*6.02*	*0.071*	*0.11*		*1*	
(3, 6, 2)		442.0+-18.0+90.0+-128.0+116.0+0.0+31.0=				533	5.49	0.725	1.16			
(3, 6, 3)		442.0+-18.0+90.0+-128.0+116.0+0.0+75.0=				577	5.70	0.602	0.96			
(3, 6, 4)		442.0+-18.0+90.0+-128.0+116.0+0.0+85.0=				587	6.32	0.705	1.13			
(3, 6, 5)		442.0+-18.0+90.0+-128.0+116.0+0.0+113.0=				615	6.98	0.913	1.46			
(3, 6, 6)		442.0+-18.0+90.0+-128.0+116.0+0.0+142.0=				644	5.20	0.054	0.09	1	1	
(3, 6, 7)		442.0+-18.0+90.0+-128.0+116.0+0.0+157.0=				659	6.93	0.754	1.20			
(3, 6, 8)		442.0+-18.0+90.0+-128.0+116.0+0.0+167.0=				669	5.97	0.578	0.92			
(3, 7, 1)						*442*	*4.64*	*0.092*	*0.15*		*1*	
(3, 7, 2)		442.0+-18.0+90.0+-128.0+128.0+0.0+31.0=				545	3.46	0.231	0.37			
(3, 7, 3)		442.0+-18.0+90.0+-128.0+128.0+0.0+75.0=				589	4.24	0.885	1.41			
(3, 7, 4)		442.0+-18.0+90.0+-128.0+128.0+0.0+85.0=				599	5.33	0.508	0.81			
(3, 7, 5)		442.0+-18.0+90.0+-128.0+128.0+0.0+113.0=				627	6.13	1.110	1.77			
(3, 7, 6)		442.0+-18.0+90.0+-128.0+128.0+0.0+142.0=				656	5.89	0.311	0.50			
(3, 7, 7)		442.0+-18.0+90.0+-128.0+128.0+0.0+157.0=				671	6.13	0.831	1.33			
(3, 7, 8)		442.0+-18.0+90.0+-128.0+128.0+0.0+167.0=				681	4.88	0.573	0.92			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
3	40	Methoxyacetic acid	25.05	90.08	1.174							
(3, 8, 1)						*448*	*6.80*	*0.134*	*0.21*			
(3, 8, 2)		442.0+-18.0+90.0+-128.0+134.0+0.0+31.0=				551	6.26	0.987	1.58			
(3, 8, 3)		442.0+-18.0+90.0+-128.0+134.0+0.0+75.0=				595	6.50	1.200	1.92			
(3, 8, 4)		442.0+-18.0+90.0+-128.0+134.0+0.0+85.0=				605	7.14	0.582	0.93			
(3, 8, 5)		442.0+-18.0+90.0+-128.0+134.0+0.0+113.0=				633	7.81	1.460	2.33			
(3, 8, 6)		442.0+-18.0+90.0+-128.0+134.0+0.0+142.0=				662	5.97	0.074	0.12		1	
(3, 8, 7)		442.0+-18.0+90.0+-128.0+134.0+0.0+157.0=				677	7.85	1.390	2.22			
(3, 8, 8)		442.0+-18.0+90.0+-128.0+134.0+0.0+167.0=				687	6.69	0.991	1.58			
					AVERAGE	*572*	*5.5*	*0.626*	*TOTAL*	*8*	*14*	
4	34	Isovaleric acid	35.59	102.13	0.937							
(4, 1, 1)						*380*	*5.57*	*0.032*	*0.04*	*1*	*1*	
(4, 1, 2)		442.0+-18.0+102.0+-128.0+66.0+0.0+31.0=				495	6.00	0.557	0.74			
(4, 1, 3)		442.0+-18.0+102.0+-128.0+66.0+0.0+75.0=				539	6.29	0.999	1.33			
(4, 1, 4)		442.0+-18.0+102.0+-128.0+66.0+0.0+85.0=				549	7.01	0.598	0.80			
(4, 1, 5)		442.0+-18.0+102.0+-128.0+66.0+0.0+113.0=				577	7.68	0.827	1.10			
(4, 1, 6)		442.0+-18.0+102.0+-128.0+66.0+0.0+142.0=				606	5.62	0.070	0.09	1	1	
(4, 1, 7)		442.0+-18.0+102.0+-128.0+66.0+0.0+157.0=				621	7.49	0.582	0.78			
(4, 1, 8)		442.0+-18.0+102.0+-128.0+66.0+0.0+167.0=				631	6.40	0.639	0.85			
(4, 2, 1)						*384*	*3.89*	*0.047*	*0.06*	*1*	*1*	
(4, 2, 2)		442.0+-18.0+102.0+-128.0+70.0+0.0+31.0=				499	4.95	1.100	1.47			
(4, 2, 3)		442.0+-18.0+102.0+-128.0+70.0+0.0+75.0=				543	5.27	1.560	2.08			
(4, 2, 4)		442.0+-18.0+102.0+-128.0+70.0+0.0+85.0=				553	6.02	0.680	0.91			
(4, 2, 5)		442.0+-18.0+102.0+-128.0+70.0+0.0+113.0=				581	6.72	0.668	0.89			
(4, 2, 6)		442.0+-18.0+102.0+-128.0+70.0+0.0+142.0=				610	4.47	0.106	0.14		1	
(4, 2, 7)		442.0+-18.0+102.0+-128.0+70.0+0.0+157.0=				625	6.61	0.569	0.76			
(4, 2, 8)		442.0+-18.0+102.0+-128.0+70.0+0.0+167.0=				635	5.54	0.889	1.19			
(4, 3, 1)						*396*	*6.32*	*0.081*	*0.11*		*1*	
(4, 3, 2)		442.0+-18.0+102.0+-128.0+82.0+0.0+31.0=				511	6.42	1.520	2.03			
(4, 3, 3)		442.0+-18.0+102.0+-128.0+82.0+0.0+75.0=				555	6.74	1.150	1.53			
(4, 3, 4)		442.0+-18.0+102.0+-128.0+82.0+0.0+85.0=				565	7.49	0.901	1.20			
(4, 3, 5)		442.0+-18.0+102.0+-128.0+82.0+0.0+113.0=				593	8.18	1.460	1.95			
(4, 3, 6)		442.0+-18.0+102.0+-128.0+82.0+0.0+142.0=				622	6.10	0.471	0.63			
(4, 3, 7)		442.0+-18.0+102.0+-128.0+82.0+0.0+157.0=				637	7.94	1.440	1.92			
(4, 3, 8)		442.0+-18.0+102.0+-128.0+82.0+0.0+167.0=				647	6.82	1.310	1.75			
(4, 4, 1)						*407*	*4.47*	*0.137*	*0.18*		*1*	
(4, 4, 2)		442.0+-18.0+102.0+-128.0+93.0+0.0+31.0=				522	5.11	1.340	1.79			
(4, 4, 3)		442.0+-18.0+102.0+-128.0+93.0+0.0+75.0=				566	5.38	1.310	1.75			
(4, 4, 4)		442.0+-18.0+102.0+-128.0+93.0+0.0+85.0=				576	6.02	0.696	0.93			
(4, 4, 5)		442.0+-18.0+102.0+-128.0+93.0+0.0+113.0=				604	6.61	0.868	1.16			
(4, 4, 6)		442.0+-18.0+102.0+-128.0+93.0+0.0+142.0=				633	4.77	0.117	0.16		1	
(4, 4, 7)		442.0+-18.0+102.0+-128.0+93.0+0.0+157.0=				648	6.53	1.080	1.44			
(4, 4, 8)		442.0+-18.0+102.0+-128.0+93.0+0.0+167.0=				658	5.65	1.010	1.35			
(4, 5, 1)						*416*	*5.97*	*0.040*	*0.05*	*1*	*1*	
(4, 5, 2)		442.0+-18.0+102.0+-128.0+102.0+0.0+31.0=				531	6.32	1.060	1.41			
(4, 5, 3)		442.0+-18.0+102.0+-128.0+102.0+0.0+75.0=				575	6.58	0.782	1.04			
(4, 5, 4)		442.0+-18.0+102.0+-128.0+102.0+0.0+85.0=				585	7.28	0.668	0.89			
(4, 5, 5)		442.0+-18.0+102.0+-128.0+102.0+0.0+113.0=				613	7.86	0.958	1.28			
(4, 5, 6)		442.0+-18.0+102.0+-128.0+102.0+0.0+142.0=				642	5.94	0.130	0.17		1	
(4, 5, 7)		442.0+-18.0+102.0+-128.0+102.0+0.0+157.0=				657	7.73	1.020	1.36			
(4, 5, 8)		442.0+-18.0+102.0+-128.0+102.0+0.0+167.0=				667	6.66	0.561	0.75			

BB#	Test #	Chemical Name	mg or uL acid	MW	d	Mass	Ret Time	LCMS Intensity	Rel Int	< 10% Rel Int	< 20% Rel Int	Mult Peaks
Table F.		Acid building blocks used in test library synthesis.										
4	34	Isovaleric acid	35.59	102.13	0.937							
(4, 6, 1)						*430*	*6.82*	*0.031*	*0.04*	*1*	*1*	
(4, 6, 2)		442.0+-18.0+102.0+-128.0+116.0+0.0+31.0=				545	6.34	0.844	1.13			
(4, 6, 3)		442.0+-18.0+102.0+-128.0+116.0+0.0+75.0=				589	6.61	0.598	0.80			
(4, 6, 4)		442.0+-18.0+102.0+-128.0+116.0+0.0+85.0=				599	7.30	0.725	0.97			
(4, 6, 5)		442.0+-18.0+102.0+-128.0+116.0+0.0+113.0=				627	7.92	0.918	1.22			
(4, 6, 6)		442.0+-18.0+102.0+-128.0+116.0+0.0+142.0=				656	6.02	0.047	0.06	1	1	
(4, 6, 7)		442.0+-18.0+102.0+-128.0+116.0+0.0+157.0=				671	7.70	1.050	1.40			
(4, 6, 8)		442.0+-18.0+102.0+-128.0+116.0+0.0+167.0=				681	6.72	0.610	0.81			
(4, 7, 1)						*442*	*4.61*	*0.121*	*0.16*		*1*	
(4, 7, 2)		442.0+-18.0+102.0+-128.0+128.0+0.0+31.0=				557	5.36	0.586	0.78			
(4, 7, 3)		442.0+-18.0+102.0+-128.0+128.0+0.0+75.0=				601	5.73	1.180	1.57			
(4, 7, 4)		442.0+-18.0+102.0+-128.0+128.0+0.0+85.0=				611	6.50	0.479	0.64			
(4, 7, 5)		442.0+-18.0+102.0+-128.0+128.0+0.0+113.0=				639	7.22	0.852	1.14			
(4, 7, 6)		442.0+-18.0+102.0+-128.0+128.0+0.0+142.0=				668	5.03	0.050	0.07	1	1	
(4, 7, 7)		442.0+-18.0+102.0+-128.0+128.0+0.0+157.0=				683	7.09	0.893	1.19			
(4, 7, 8)		442.0+-18.0+102.0+-128.0+128.0+0.0+167.0=				693	5.89	1.010	1.35			
(4, 8, 1)						*448*	*6.85*	*0.029*	*0.04*	*1*	*1*	
(4, 8, 2)		442.0+-18.0+102.0+-128.0+134.0+0.0+31.0=				563	7.12	1.160	1.55			
(4, 8, 3)		442.0+-18.0+102.0+-128.0+134.0+0.0+75.0=				607	7.41	1.310	1.75			
(4, 8, 4)		442.0+-18.0+102.0+-128.0+134.0+0.0+85.0=				617	8.08	0.963	1.28			
(4, 8, 5)		442.0+-18.0+102.0+-128.0+134.0+0.0+113.0=				645	8.72	1.700	2.27			
(4, 8, 6)		442.0+-18.0+102.0+-128.0+134.0+0.0+142.0=				674	6.72	0.084	0.11		1	
(4, 8, 7)		442.0+-18.0+102.0+-128.0+134.0+0.0+157.0=				689	8.45	1.740	2.32			
(4, 8, 8)		442.0+-18.0+102.0+-128.0+134.0+0.0+167.0=				699	7.44	0.979	1.31			
				AVERAGE		*583*	*6.5*	*0.750*	*TOTAL*	*8*	*15*	
5	31	Hexadienoic acid, 2,4-	36.61	112.13	1.000							
(5, 1, 1)						*380*	*5.62*	*0.033*	*0.09*	*1*	*1*	
(5, 1, 2)		442.0+-18.0+112.0+-128.0+66.0+0.0+31.0=				505	6.05	0.311	0.85			2
(5, 1, 3)		442.0+-18.0+112.0+-128.0+66.0+0.0+75.0=				549	6.23	0.406	1.11			
(5, 1, 4)		442.0+-18.0+112.0+-128.0+66.0+0.0+85.0=				559	6.93	0.270	0.74			
(5, 1, 5)		442.0+-18.0+112.0+-128.0+66.0+0.0+113.0=				587	7.65	0.463	1.27			
(5, 1, 6)		442.0+-18.0+112.0+-128.0+66.0+0.0+142.0=				616	5.51	0.050	0.14		1	
(5, 1, 7)		442.0+-18.0+112.0+-128.0+66.0+0.0+157.0=				631	7.46	0.520	1.42			
(5, 1, 8)		442.0+-18.0+112.0+-128.0+66.0+0.0+167.0=				641	6.34	0.393	1.07			
(5, 2, 1)						*384*	*3.97*	*0.031*	*0.08*	*1*	*1*	
(5, 2, 2)		442.0+-18.0+112.0+-128.0+70.0+0.0+31.0=				509	6.98	0.532	1.45			2
(5, 2, 3)		442.0+-18.0+112.0+-128.0+70.0+0.0+75.0=				553	5.25	0.365	1.00			
(5, 2, 4)		442.0+-18.0+112.0+-128.0+70.0+0.0+85.0=				563	5.94	0.262	0.72			
(5, 2, 5)		442.0+-18.0+112.0+-128.0+70.0+0.0+113.0=				591	6.63	0.401	1.10			
(5, 2, 6)		442.0+-18.0+112.0+-128.0+70.0+0.0+142.0=				620	4.42	0.036	0.10		1	
(5, 2, 7)		442.0+-18.0+112.0+-128.0+70.0+0.0+157.0=				635	6.53	0.356	0.97			
(5, 2, 8)		442.0+-18.0+112.0+-128.0+70.0+0.0+167.0=				645	5.49	0.397	1.08			
(5, 3, 1)						*396*	*6.07*	*0.073*	*0.20*			
(5, 3, 2)		442.0+-18.0+112.0+-128.0+82.0+0.0+31.0=				521	6.45	0.602	1.64			
(5, 3, 3)		442.0+-18.0+112.0+-128.0+82.0+0.0+75.0=				565	6.66	0.573	1.57			
(5, 3, 4)		442.0+-18.0+112.0+-128.0+82.0+0.0+85.0=				575	7.41	0.324	0.89			
(5, 3, 5)		442.0+-18.0+112.0+-128.0+82.0+0.0+113.0=				603	8.16	0.692	1.89			
(5, 3, 6)		442.0+-18.0+112.0+-128.0+82.0+0.0+142.0=				632	5.91	0.078	0.21			
(5, 3, 7)		442.0+-18.0+112.0+-128.0+82.0+0.0+157.0=				647	7.92	0.905	2.47			
(5, 3, 8)		442.0+-18.0+112.0+-128.0+82.0+0.0+167.0=				657	6.74	0.836	2.28			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
5	31	Hexadienoic acid, 2,4-	[redacted]	112.13	1.000							
(5, 4, 1)						407	4.50	0.143	0.39			
(5, 4, 2)		442.0+-18.0+112.0+-128.0+93.0+0.0+31.0=				532	5.22	0.344	0.94			
(5, 4, 3)		442.0+-18.0+112.0+-128.0+93.0+0.0+75.0=				576	5.33	0.463	1.27			
(5, 4, 4)		442.0+-18.0+112.0+-128.0+93.0+0.0+85.0=				586	5.94	0.266	0.73			
(5, 4, 5)		442.0+-18.0+112.0+-128.0+93.0+0.0+113.0=				614	6.53	0.352	0.96			
(5, 4, 6)		442.0+-18.0+112.0+-128.0+93.0+0.0+142.0=				643	4.71	0.051	0.14		1	
(5, 4, 7)		442.0+-18.0+112.0+-128.0+93.0+0.0+157.0=				658	6.47	0.455	1.24			
(5, 4, 8)		442.0+-18.0+112.0+-128.0+93.0+0.0+167.0=				668	5.57	0.492	1.34			
(5, 5, 1)						416	1.51	0.040	0.11		1	
(5, 5, 2)		442.0+-18.0+112.0+-128.0+102.0+0.0+31.0=				541	6.34	0.430	1.17			
(5, 5, 3)		442.0+-18.0+112.0+-128.0+102.0+0.0+75.0=				585	6.50	0.385	1.05			
(5, 5, 4)		442.0+-18.0+112.0+-128.0+102.0+0.0+85.0=				595	7.17	0.251	0.69			
(5, 5, 5)		442.0+-18.0+112.0+-128.0+102.0+0.0+113.0=				623	7.84	0.508	1.39			
(5, 5, 6)		442.0+-18.0+112.0+-128.0+102.0+0.0+142.0=				652	5.14	0.307	0.84			
(5, 5, 7)		442.0+-18.0+112.0+-128.0+102.0+0.0+157.0=				667	7.70	0.737	2.01			
(5, 5, 8)		442.0+-18.0+112.0+-128.0+102.0+0.0+167.0=				677	6.58	0.414	1.13			
(5, 6, 1)						430	6.07	0.057	0.15		1	
(5, 6, 2)		442.0+-18.0+112.0+-128.0+116.0+0.0+31.0=				555	6.39	0.319	0.87			2
(5, 6, 3)		442.0+-18.0+112.0+-128.0+116.0+0.0+75.0=				599	6.55	0.418	1.14			
(5, 6, 4)		442.0+-18.0+112.0+-128.0+116.0+0.0+85.0=				609	7.20	0.217	0.59			
(5, 6, 5)		442.0+-18.0+112.0+-128.0+116.0+0.0+113.0=				637	7.84	0.430	1.17			
(5, 6, 6)		442.0+-18.0+112.0+-128.0+116.0+0.0+142.0=				666	5.94	0.034	0.09	1	1	2
(5, 6, 7)		442.0+-18.0+112.0+-128.0+116.0+0.0+157.0=				681	7.68	0.582	1.59			
(5, 6, 8)		442.0+-18.0+112.0+-128.0+116.0+0.0+167.0=				691	6.63	0.410	1.12			
(5, 7, 1)						442	4.63	0.115	0.31			
(5, 7, 2)		442.0+-18.0+112.0+-128.0+128.0+0.0+31.0=				567	5.43	0.232	0.63			
(5, 7, 3)		442.0+-18.0+112.0+-128.0+128.0+0.0+75.0=				611	5.65	0.446	1.22			
(5, 7, 4)		442.0+-18.0+112.0+-128.0+128.0+0.0+85.0=				621	6.42	0.191	0.52			
(5, 7, 5)		442.0+-18.0+112.0+-128.0+128.0+0.0+113.0=				649	7.17	0.426	1.16			
(5, 7, 6)		442.0+-18.0+112.0+-128.0+128.0+0.0+142.0=				678	4.77	0.028	0.08	1	1	
(5, 7, 7)		442.0+-18.0+112.0+-128.0+128.0+0.0+157.0=				693	6.98	0.639	1.75			
(5, 7, 8)		442.0+-18.0+112.0+-128.0+128.0+0.0+167.0=				703	5.78	0.467	1.28			
(5, 8, 1)						448	6.82	0.067	0.18		1	
(5, 8, 2)		442.0+-18.0+112.0+-128.0+134.0+0.0+31.0=				573	7.12	0.594	1.62			
(5, 8, 3)		442.0+-18.0+112.0+-128.0+134.0+0.0+75.0=				617	7.33	0.487	1.33			
(5, 8, 4)		442.0+-18.0+112.0+-128.0+134.0+0.0+85.0=				627	8.02	0.426	1.16			
(5, 8, 5)		442.0+-18.0+112.0+-128.0+134.0+0.0+113.0=				655	8.69	0.733	2.00			
(5, 8, 6)		442.0+-18.0+112.0+-128.0+134.0+0.0+142.0=				684	6.71	0.035	0.09	1	1	
(5, 8, 7)		442.0+-18.0+112.0+-128.0+134.0+0.0+157.0=				699	8.45	0.827	2.26			
(5, 8, 8)		442.0+-18.0+112.0+-128.0+134.0+0.0+167.0=				709	7.38	0.696	1.90			
					AVERAGE	591	6.4	0.366	TOTAL	5	11	
6	33	Isonicotinic acid	[redacted]	123.11	1.000							
(6, 1, 1)						380	5.60	0.044	0.10		1	
(6, 1, 2)		442.0+-18.0+123.0+-128.0+66.0+0.0+31.0=				516	5.28	0.438	0.98			
(6, 1, 3)		442.0+-18.0+123.0+-128.0+66.0+0.0+75.0=				560	5.44	0.512	1.15			
(6, 1, 4)		442.0+-18.0+123.0+-128.0+66.0+0.0+85.0=				570	6.10	0.206	0.46			
(6, 1, 5)		442.0+-18.0+123.0+-128.0+66.0+0.0+113.0=				598	6.85	0.459	1.03			
(6, 1, 6)		442.0+-18.0+123.0+-128.0+66.0+0.0+142.0=				627	5.22	0.015	0.03	1	1	
(6, 1, 7)		442.0+-18.0+123.0+-128.0+66.0+0.0+157.0=				642	6.77	0.360	0.81			
(6, 1, 8)		442.0+-18.0+123.0+-128.0+66.0+0.0+167.0=				652	5.65	0.442	0.99			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
6	33	Isonicotinic acid	0.0320	123.11	1.000							
(6, 2, 1)						*384*	*4.45*	*0.030*	*0.07*	*1*	*1*	*2*
(6, 2, 2)		442.0+-18.0+123.0+-128.0+70.0+0.0+31.0=				520	3.30	0.319	0.72			
(6, 2, 3)		442.0+-18.0+123.0+-128.0+70.0+0.0+75.0=				564	3.83	0.565	1.27			
(6, 2, 4)		442.0+-18.0+123.0+-128.0+70.0+0.0+85.0=				574	5.01	0.553	1.24			
(6, 2, 5)		442.0+-18.0+123.0+-128.0+70.0+0.0+113.0=				602	5.78	0.532	1.19			
(6, 2, 6)		442.0+-18.0+123.0+-128.0+70.0+0.0+142.0=				631	2.98	0.029	0.06	1	1	
(6, 2, 7)		442.0+-18.0+123.0+-128.0+70.0+0.0+157.0=				646	5.73	0.377	0.85			
(6, 2, 8)		442.0+-18.0+123.0+-128.0+70.0+0.0+167.0=				656	4.55	0.606	1.36			
(6, 3, 1)						*396*	*6.08*	*0.053*	*0.12*		*1*	*3*
(6, 3, 2)		442.0+-18.0+123.0+-128.0+82.0+0.0+31.0=				532	5.73	0.717	1.61			
(6, 3, 3)		442.0+-18.0+123.0+-128.0+82.0+0.0+75.0=				576	5.97	0.905	2.03			
(6, 3, 4)		442.0+-18.0+123.0+-128.0+82.0+0.0+85.0=				586	6.61	0.844	1.89			
(6, 3, 5)		442.0+-18.0+123.0+-128.0+82.0+0.0+113.0=				614	7.41	1.040	2.33			
(6, 3, 6)		442.0+-18.0+123.0+-128.0+82.0+0.0+142.0=				643	5.76	0.042	0.09	1	1	
(6, 3, 7)		442.0+-18.0+123.0+-128.0+82.0+0.0+157.0=				658	7.25	0.799	1.79			
(6, 3, 8)		442.0+-18.0+123.0+-128.0+82.0+0.0+167.0=				668	6.10	0.750	1.68			
(6, 4, 1)						*407*	*4.47*	*0.108*	*0.24*			
(6, 4, 2)		442.0+-18.0+123.0+-128.0+93.0+0.0+31.0=				543	2.37	0.754	1.69			3
(6, 4, 3)		442.0+-18.0+123.0+-128.0+93.0+0.0+75.0=				587	4.34	0.795	1.78			
(6, 4, 4)		442.0+-18.0+123.0+-128.0+93.0+0.0+85.0=				597	5.17	0.733	1.64			
(6, 4, 5)		442.0+-18.0+123.0+-128.0+93.0+0.0+113.0=				625	5.81	0.557	1.25			
(6, 4, 6)		442.0+-18.0+123.0+-128.0+93.0+0.0+142.0=				654	3.70	0.031	0.07	1	1	
(6, 4, 7)		442.0+-18.0+123.0+-128.0+93.0+0.0+157.0=				669	5.81	0.520	1.17			
(6, 4, 8)		442.0+-18.0+123.0+-128.0+93.0+0.0+167.0=				679	4.82	0.766	1.72			
(6, 5, 1)						*416*	*6.00*	*0.047*	*0.11*		*1*	
(6, 5, 2)		442.0+-18.0+123.0+-128.0+102.0+0.0+31.0=				552	5.73	0.295	0.66			
(6, 5, 3)		442.0+-18.0+123.0+-128.0+102.0+0.0+75.0=				596	5.92	0.483	1.08			
(6, 5, 4)		442.0+-18.0+123.0+-128.0+102.0+0.0+85.0=				606	6.50	0.516	1.16			
(6, 5, 5)		442.0+-18.0+123.0+-128.0+102.0+0.0+113.0=				634	7.17	0.606	1.36			
(6, 5, 6)		442.0+-18.0+123.0+-128.0+102.0+0.0+142.0=				663	5.70	0.037	0.08	1	1	2
(6, 5, 7)		442.0+-18.0+123.0+-128.0+102.0+0.0+157.0=				678	7.09	0.532	1.19			
(6, 5, 8)		442.0+-18.0+123.0+-128.0+102.0+0.0+167.0=				688	6.10	0.459	1.03			
(6, 6, 1)						*430*	*6.08*	*0.042*	*0.09*	*1*	*1*	
(6, 6, 2)		442.0+-18.0+123.0+-128.0+116.0+0.0+31.0=				566	5.84	0.324	0.73			
(6, 6, 3)		442.0+-18.0+123.0+-128.0+116.0+0.0+75.0=				610	5.97	0.573	1.28			
(6, 6, 4)		442.0+-18.0+123.0+-128.0+116.0+0.0+85.0=				620	6.50	0.455	1.02			
(6, 6, 5)		442.0+-18.0+123.0+-128.0+116.0+0.0+113.0=				648	7.20	0.627	1.41			
(6, 6, 6)		442.0+-18.0+123.0+-128.0+116.0+0.0+142.0=				677	5.65	0.023	0.05	1	1	
(6, 6, 7)		442.0+-18.0+123.0+-128.0+116.0+0.0+157.0=				692	7.12	0.594	1.33			
(6, 6, 8)		442.0+-18.0+123.0+-128.0+116.0+0.0+167.0=				702	6.18	0.512	1.15			
(6, 7, 1)						*442*	*4.66*	*0.087*	*0.20*			
(6, 7, 2)		442.0+-18.0+123.0+-128.0+128.0+0.0+31.0=				578	4.02	0.242	0.54			
(6, 7, 3)		442.0+-18.0+123.0+-128.0+128.0+0.0+75.0=				622	4.42	0.631	1.41			
(6, 7, 4)		442.0+-18.0+123.0+-128.0+128.0+0.0+85.0=				632	5.73	0.717	1.61			
(6, 7, 5)		442.0+-18.0+123.0+-128.0+128.0+0.0+113.0=				660	6.21	0.553	1.24			
(6, 7, 6)		442.0+-18.0+123.0+-128.0+128.0+0.0+142.0=				689	3.81	0.017	0.04	1	1	
(6, 7, 7)		442.0+-18.0+123.0+-128.0+128.0+0.0+157.0=				704	6.16	0.414	0.93			
(6, 7, 8)		442.0+-18.0+123.0+-128.0+128.0+0.0+167.0=				714	4.88	0.369	0.83			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
6	33	Isonicotinic acid	[redacted]	123.11	1.000							
(6, 8, 1)						448	6.80	0.069	0.15		1	
(6, 8, 2)		442.0+-18.0+123.0+-128.0+134.0+0.0+31.0=				584	6.64	0.647	1.45			
(6, 8, 3)		442.0+-18.0+123.0+-128.0+134.0+0.0+75.0=				628	6.80	0.770	1.73			
(6, 8, 4)		442.0+-18.0+123.0+-128.0+134.0+0.0+85.0=				638	7.41	0.455	1.02			
(6, 8, 5)		442.0+-18.0+123.0+-128.0+134.0+0.0+113.0=				666	8.10	0.877	1.97			
(6, 8, 6)		442.0+-18.0+123.0+-128.0+134.0+0.0+142.0=				695	6.80	0.030	0.07	1	1	2
(6, 8, 7)		442.0+-18.0+123.0+-128.0+134.0+0.0+157.0=				710	8.00	1.060	2.38			
(6, 8, 8)		442.0+-18.0+123.0+-128.0+134.0+0.0+167.0=				720	6.96	0.598	1.34			
		AVERAGE				601	5.8	0.446	TOTAL	10	14	
7	45	Methoxyphenylacetic acid, 4-	[redacted]	166.18	1.000							
(7, 1, 1)						380	5.54	0.035	0.06	1	1	
(7, 1, 2)		442.0+-18.0+166.0+-128.0+66.0+0.0+31.0=				559	6.00	0.430	0.71			
(7, 1, 3)		442.0+-18.0+166.0+-128.0+66.0+0.0+75.0=				603	6.21	0.659	1.09			
(7, 1, 4)		442.0+-18.0+166.0+-128.0+66.0+0.0+85.0=				613	6.87	0.352	0.58			
(7, 1, 5)		442.0+-18.0+166.0+-128.0+66.0+0.0+113.0=				641	7.46	0.795	1.31			
(7, 1, 6)		442.0+-18.0+166.0+-128.0+66.0+0.0+142.0=				670	5.65	0.033	0.05	1	1	
(7, 1, 7)		442.0+-18.0+166.0+-128.0+66.0+0.0+157.0=				685	7.38	0.422	0.70			
(7, 1, 8)		442.0+-18.0+166.0+-128.0+66.0+0.0+167.0=				695	6.37	0.467	0.77			
(7, 2, 1)						384	5.70	0.068	0.11		1	2
(7, 2, 2)		442.0+-18.0+166.0+-128.0+70.0+0.0+31.0=				563	5.06	0.872	1.44			
(7, 2, 3)		442.0+-18.0+166.0+-128.0+70.0+0.0+75.0=				607	5.30	1.200	1.98			
(7, 2, 4)		442.0+-18.0+166.0+-128.0+70.0+0.0+85.0=				617	5.97	0.504	0.83			
(7, 2, 5)		442.0+-18.0+166.0+-128.0+70.0+0.0+113.0=				645	6.55	0.659	1.09			
(7, 2, 6)		442.0+-18.0+166.0+-128.0+70.0+0.0+142.0=				674	4.74	0.050	0.08	1	1	
(7, 2, 7)		442.0+-18.0+166.0+-128.0+70.0+0.0+157.0=				689	6.53	0.508	0.84			
(7, 2, 8)		442.0+-18.0+166.0+-128.0+70.0+0.0+167.0=				699	5.59	0.651	1.07			
(7, 3, 1)						396	7.67	0.397	0.66			
(7, 3, 2)		442.0+-18.0+166.0+-128.0+82.0+0.0+31.0=				575	6.39	1.050	1.73			
(7, 3, 3)		442.0+-18.0+166.0+-128.0+82.0+0.0+75.0=				619	6.63	1.080	1.78			
(7, 3, 4)		442.0+-18.0+166.0+-128.0+82.0+0.0+85.0=				629	7.33	0.659	1.09			
(7, 3, 5)		442.0+-18.0+166.0+-128.0+82.0+0.0+113.0=				657	7.94	1.640	2.71			
(7, 3, 6)		442.0+-18.0+166.0+-128.0+82.0+0.0+142.0=				686	6.05	0.087	0.14		1	
(7, 3, 7)		442.0+-18.0+166.0+-128.0+82.0+0.0+157.0=				701	7.78	1.390	2.29			
(7, 3, 8)		442.0+-18.0+166.0+-128.0+82.0+0.0+167.0=				711	6.74	0.495	0.82			
(7, 4, 1)						407	4.45	0.161	0.27			
(7, 4, 2)		442.0+-18.0+166.0+-128.0+93.0+0.0+31.0=				586	5.19	0.651	1.07			
(7, 4, 3)		442.0+-18.0+166.0+-128.0+93.0+0.0+75.0=				630	5.41	0.991	1.64			
(7, 4, 4)		442.0+-18.0+166.0+-128.0+93.0+0.0+85.0=				640	6.00	0.537	0.89			
(7, 4, 5)		442.0+-18.0+166.0+-128.0+93.0+0.0+113.0=				668	6.47	0.717	1.18			
(7, 4, 6)		442.0+-18.0+166.0+-128.0+93.0+0.0+142.0=				697	4.90	0.043	0.07	1	1	
(7, 4, 7)		442.0+-18.0+166.0+-128.0+93.0+0.0+157.0=				712	6.47	0.647	1.07			
(7, 4, 8)		442.0+-18.0+166.0+-128.0+93.0+0.0+167.0=				722	5.65	0.766	1.26			
(7, 5, 1)						416	5.97	0.050	0.08	1	1	
(7, 5, 2)		442.0+-18.0+166.0+-128.0+102.0+0.0+31.0=				595	6.26	0.680	1.12			
(7, 5, 3)		442.0+-18.0+166.0+-128.0+102.0+0.0+75.0=				639	6.47	0.713	1.18			
(7, 5, 4)		442.0+-18.0+166.0+-128.0+102.0+0.0+85.0=				649	7.11	0.590	0.97			
(7, 5, 5)		442.0+-18.0+166.0+-128.0+102.0+0.0+113.0=				677	7.65	1.050	1.73			
(7, 5, 6)		442.0+-18.0+166.0+-128.0+102.0+0.0+142.0=				706	5.91	0.060	0.10		1	
(7, 5, 7)		442.0+-18.0+166.0+-128.0+102.0+0.0+157.0=				721	7.57	0.664	1.10			
(7, 5, 8)		442.0+-18.0+166.0+-128.0+102.0+0.0+167.0=				731	6.61	0.520	0.86			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
7	45	Methoxyphenylacetic acid, 4-	[redacted]	166.18	1.000							
(7, 6, 1)						*430*	*6.74*	*0.040*	*0.07*	*1*	*1*	
(7, 6, 2)		442.0+-18.0+166.0+-128.0+116.0+0.0+31.0=				609	6.31	0.610	1.01			
(7, 6, 3)		442.0+-18.0+166.0+-128.0+116.0+0.0+75.0=				653	6.53	0.647	1.07			
(7, 6, 4)		442.0+-18.0+166.0+-128.0+116.0+0.0+85.0=				663	7.14	0.598	0.99			
(7, 6, 5)		442.0+-18.0+166.0+-128.0+116.0+0.0+113.0=				691	7.67	0.975	1.61			
(7, 6, 6)		442.0+-18.0+166.0+-128.0+116.0+0.0+142.0=				720	6.00	0.264	0.44			
(7, 6, 7)		442.0+-18.0+166.0+-128.0+116.0+0.0+157.0=				735	7.57	0.930	1.53			
(7, 6, 8)		442.0+-18.0+166.0+-128.0+116.0+0.0+167.0=				745	6.66	0.483	0.80			
(7, 7, 1)						*442*	*4.58*	*0.115*	*0.19*		*1*	
(7, 7, 2)		442.0+-18.0+166.0+-128.0+128.0+0.0+31.0=				621	5.43	0.442	0.73			
(7, 7, 3)		442.0+-18.0+166.0+-128.0+128.0+0.0+75.0=				665	5.70	0.975	1.61			
(7, 7, 4)		442.0+-18.0+166.0+-128.0+128.0+0.0+85.0=				675	6.42	0.315	0.52			
(7, 7, 5)		442.0+-18.0+166.0+-128.0+128.0+0.0+113.0=				703	7.01	0.844	1.39			
(7, 7, 6)		442.0+-18.0+166.0+-128.0+128.0+0.0+142.0=				732	5.09	0.020	0.03	1	1	
(7, 7, 7)		442.0+-18.0+166.0+-128.0+128.0+0.0+157.0=				747	6.93	0.848	1.40			
(7, 7, 8)		442.0+-18.0+166.0+-128.0+128.0+0.0+167.0=				757	5.89	0.627	1.03			
(7, 8, 1)						*448*	*6.82*	*0.049*	*0.08*	*1*	*1*	
(7, 8, 2)		442.0+-18.0+166.0+-128.0+134.0+0.0+31.0=				627	7.06	0.987	1.63			
(7, 8, 3)		442.0+-18.0+166.0+-128.0+134.0+0.0+75.0=				671	7.27	1.390	2.29			
(7, 8, 4)		442.0+-18.0+166.0+-128.0+134.0+0.0+85.0=				681	7.89	0.786	1.30			
(7, 8, 5)		442.0+-18.0+166.0+-128.0+134.0+0.0+113.0=				709	8.45	1.380	2.28			
(7, 8, 6)		442.0+-18.0+166.0+-128.0+134.0+0.0+142.0=				738	6.71	0.054	0.09	1	1	
(7, 8, 7)		442.0+-18.0+166.0+-128.0+134.0+0.0+157.0=				753	8.26	1.360	2.24			
(7, 8, 8)		442.0+-18.0+166.0+-128.0+134.0+0.0+167.0=				763	7.35	0.725	1.20			
					AVERAGE	*639*	*6.5*	*0.606*	*TOTAL*	*9*	*13*	
8	49	Methyl terephthalate, mono-	[redacted]	180.16	1.000							
(8, 1, 1)						*380*	*5.60*	*0.023*	*0.04*	*1*	*1*	
(8, 1, 2)		442.0+-18.0+180.0+-128.0+66.0+0.0+31.0=				573	6.00	0.442	0.78			
(8, 1, 3)		442.0+-18.0+180.0+-128.0+66.0+0.0+75.0=				617	6.10	0.676	1.19			
(8, 1, 4)		442.0+-18.0+180.0+-128.0+66.0+0.0+85.0=				627	6.74	0.389	0.69			
(8, 1, 5)		442.0+-18.0+180.0+-128.0+66.0+0.0+113.0=				655	7.33	0.688	1.22			
(8, 1, 6)		442.0+-18.0+180.0+-128.0+66.0+0.0+142.0=				684	5.57	0.050	0.09	1	1	
(8, 1, 7)		442.0+-18.0+180.0+-128.0+66.0+0.0+157.0=				699	7.17	0.492	0.87			
(8, 1, 8)		442.0+-18.0+180.0+-128.0+66.0+0.0+167.0=				709	6.18	0.500	0.88			
(8, 2, 1)						*384*	*5.62*	*0.063*	*0.11*		*1*	*2*
(8, 2, 2)		442.0+-18.0+180.0+-128.0+70.0+0.0+31.0=				577	5.17	0.864	1.53			
(8, 2, 3)		442.0+-18.0+180.0+-128.0+70.0+0.0+75.0=				621	5.28	0.713	1.26			
(8, 2, 4)		442.0+-18.0+180.0+-128.0+70.0+0.0+85.0=				631	5.92	0.578	1.02			2
(8, 2, 5)		442.0+-18.0+180.0+-128.0+70.0+0.0+113.0=				659	6.50	0.573	1.01			
(8, 2, 6)		442.0+-18.0+180.0+-128.0+70.0+0.0+142.0=				688	4.53	0.069	0.12		1	
(8, 2, 7)		442.0+-18.0+180.0+-128.0+70.0+0.0+157.0=				703	6.37	0.442	0.78			
(8, 2, 8)		442.0+-18.0+180.0+-128.0+70.0+0.0+167.0=				713	5.46	0.553	0.98			
(8, 3, 1)						*396*	*6.08*	*0.103*	*0.18*		*1*	*2*
(8, 3, 2)		442.0+-18.0+180.0+-128.0+82.0+0.0+31.0=				589	6.40	0.532	0.94			
(8, 3, 3)		442.0+-18.0+180.0+-128.0+82.0+0.0+75.0=				633	6.56	0.926	1.64			
(8, 3, 4)		442.0+-18.0+180.0+-128.0+82.0+0.0+85.0=				643	7.17	0.930	1.64			
(8, 3, 5)		442.0+-18.0+180.0+-128.0+82.0+0.0+113.0=				671	7.78	1.690	2.99			
(8, 3, 6)		442.0+-18.0+180.0+-128.0+82.0+0.0+142.0=				700	5.94	0.150	0.27			
(8, 3, 7)		442.0+-18.0+180.0+-128.0+82.0+0.0+157.0=				715	7.60	1.030	1.82			
(8, 3, 8)		442.0+-18.0+180.0+-128.0+82.0+0.0+167.0=				725	6.58	0.639	1.13			

Table F.		Acid building blocks used in test library synthesis.										
	Test		mg or uL				Ret	LCMS	Rel	< 10%	< 20%	Mult
BB#	#	Chemical Name	acid	MW	d	Mass	Time	Intensity	Int	Rel Int	Rel Int	Peaks
8	49	Methyl terephthalate, mono-	53.82	180.16	1.000							
(8, 4, 1)						*407*	*4.42*	*0.164*	*0.29*			
(8, 4, 2)		442.0+-18.0+180.0+-128.0+93.0+0.0+31.0=				600	5.28	0.553	0.98			
(8, 4, 3)		442.0+-18.0+180.0+-128.0+93.0+0.0+75.0=				644	5.36	0.897	1.58			
(8, 4, 4)		442.0+-18.0+180.0+-128.0+93.0+0.0+85.0=				654	5.92	0.668	1.18			
(8, 4, 5)		442.0+-18.0+180.0+-128.0+93.0+0.0+113.0=				682	6.42	0.729	1.29			
(8, 4, 6)		442.0+-18.0+180.0+-128.0+93.0+0.0+142.0=				711	4.80	0.070	0.12		1	
(8, 4, 7)		442.0+-18.0+180.0+-128.0+93.0+0.0+157.0=				726	6.34	0.676	1.19			
(8, 4, 8)		442.0+-18.0+180.0+-128.0+93.0+0.0+167.0=				736	5.54	0.627	1.11			
(8, 5, 1)						*416*	*5.97*	*0.052*	*0.09*	*1*	*1*	
(8, 5, 2)		442.0+-18.0+180.0+-128.0+102.0+0.0+31.0=				609	6.29	0.532	0.94			
(8, 5, 3)		442.0+-18.0+180.0+-128.0+102.0+0.0+75.0=				653	6.40	0.430	0.76			
(8, 5, 4)		442.0+-18.0+180.0+-128.0+102.0+0.0+85.0=				663	6.96	0.668	1.18			
(8, 5, 5)		442.0+-18.0+180.0+-128.0+102.0+0.0+113.0=				691	7.52	1.010	1.78			
(8, 5, 6)		442.0+-18.0+180.0+-128.0+102.0+0.0+142.0=				720	5.86	0.088	0.16		1	
(8, 5, 7)		442.0+-18.0+180.0+-128.0+102.0+0.0+157.0=				735	7.38	0.733	1.30			
(8, 5, 8)		442.0+-18.0+180.0+-128.0+102.0+0.0+167.0=				745	6.45	0.299	0.53			
(8, 6, 1)						*430*	*6.02*	*0.068*	*0.12*		*1*	*2*
(8, 6, 2)		442.0+-18.0+180.0+-128.0+116.0+0.0+31.0=				623	6.40	0.291	0.51			
(8, 6, 3)		442.0+-18.0+180.0+-128.0+116.0+0.0+75.0=				667	6.50	0.668	1.18			
(8, 6, 4)		442.0+-18.0+180.0+-128.0+116.0+0.0+85.0=				677	7.04	0.786	1.39			
(8, 6, 5)		442.0+-18.0+180.0+-128.0+116.0+0.0+113.0=				705	7.62	0.979	1.73			
(8, 6, 6)		442.0+-18.0+180.0+-128.0+116.0+0.0+142.0=				734	6.00	0.050	0.09	1	1	
(8, 6, 7)		442.0+-18.0+180.0+-128.0+116.0+0.0+157.0=				749	7.46	0.795	1.40			
(8, 6, 8)		442.0+-18.0+180.0+-128.0+116.0+0.0+167.0=				759	6.58	0.332	0.59			
(8, 7, 1)						*442*	*4.56*	*0.117*	*0.21*			
(8, 7, 2)		442.0+-18.0+180.0+-128.0+128.0+0.0+31.0=				635	5.44	0.389	0.69			
(8, 7, 3)		442.0+-18.0+180.0+-128.0+128.0+0.0+75.0=				679	0.56	1.020	1.80			
(8, 7, 4)		442.0+-18.0+180.0+-128.0+128.0+0.0+85.0=				689	6.24	0.459	0.81			
(8, 7, 5)		442.0+-18.0+180.0+-128.0+128.0+0.0+113.0=				717	6.88	0.987	1.74			
(8, 7, 6)		442.0+-18.0+180.0+-128.0+128.0+0.0+142.0=				746	4.85	0.030	0.05	1	1	
(8, 7, 7)		442.0+-18.0+180.0+-128.0+128.0+0.0+157.0=				761	6.69	0.553	0.98			
(8, 7, 8)		442.0+-18.0+180.0+-128.0+128.0+0.0+167.0=				771	5.68	0.516	0.91			
(8, 8, 1)						*448*	*6.77*	*0.120*	*0.21*			
(8, 8, 2)		442.0+-18.0+180.0+-128.0+134.0+0.0+31.0=				641	7.12	0.938	1.66			
(8, 8, 3)		442.0+-18.0+180.0+-128.0+134.0+0.0+75.0=				685	7.25	1.160	2.05			
(8, 8, 4)		442.0+-18.0+180.0+-128.0+134.0+0.0+85.0=				695	7.84	0.979	1.73			
(8, 8, 5)		442.0+-18.0+180.0+-128.0+134.0+0.0+113.0=				723	8.37	1.290	2.28			
(8, 8, 6)		442.0+-18.0+180.0+-128.0+134.0+0.0+142.0=				752	6.72	0.056	0.10		1	2
(8, 8, 7)		442.0+-18.0+180.0+-128.0+134.0+0.0+157.0=				767	8.16	1.180	2.08			
(8, 8, 8)		442.0+-18.0+180.0+-128.0+134.0+0.0+167.0=				777	7.28	0.602	1.06			
					AVERAGE	*651*	*6.3*	*0.557*	*TOTAL*	*5*	*12*	
									SUBTOTAL	*58*	*97*	
									less redundant butyrolactone misses	*-20*	*-41*	
									GRAND TOTAL	*38*	*56*	
									total compounds	*456*	*456*	
									% HITS	*91.7*	*87.7*	

Table G.	Spacer, epoxycyclohexenol, and nitrone building blocks used in library synthesis.
BB#	Chemical Name
	Spacer Postion 1
1	SKIP CODON
2	Glycine
3	6-Aminocaproic acid
	Epoxycyclohexenol Position 2
1	(+)-Epoxycyclohexenol
2	(-)-Epoxycyclohexenol
	Nitrone Position 3
1	2-Iodobenzyl nitrone
2	3-Iodobenzyl nitrone
3	4-Iodobenzyl nitrone

Table H.		Alkyne building blocks used in library synthesis.						
		mono terminal alkyne	417.0	umol alkyne				
		bis terminal alkyne (italicized)	1042.6	umol alkyne				
		* BB #23 was tested separately in an NMR scale reaction (data not shown)						
	Test		mg or uL					
BB#	#	Chemical Name	alkyne	MW	d	Vendor	Catalog #	Size
1	±1	Acetaldehyde ethyl propargyl acetal	59.5	128.17	0.898	Aldrich	33,482-0	25 g
2	±2	Butyl 1-methyl-2-propynyl ether, tert-	56.2	126.20	0.795	Aldrich	38,425-9	100 mL
3	3	Butyl)phenylacetylene, 4-(tert-	74.1	158.00	0.889	GFS	115730	10 g
4	±5,43	Butynloxy)tetrahydro-2H-pyran, 2-(3-	65.4	154.21	0.984	Aldrich	30,586-3	5 g
5	6	Chloro-4-ethynylbenzene, 1-	57.0	136.58	1.000	Aldrich	20,647-4	1 g
6	8	Decadiyne, 1,5-	56.0	134.22	1.000	GFS	126706	10 g
7	*10*	*Diethynylbenzene, m-*	*131.5*	*126.15*	*1.000*	GFS	*130100*	*5 g*
8	11	Dimethyl-1-butyne, 3,3-	51.4	82.15	0.667	Aldrich	24,439-2	5 g
9	12	Dimethylamino-2-propyne, 1-	44.9	83.13	0.772	Aldrich	14,306-5	5 g
10	13	Dodecyne, 1-	89.1	166.31	0.778	Aldrich	24,440-6	5 g
11	46	Ethynyl-1-cyclohexanol, 1-	53.6	124.18	0.967	Aldrich	E5,140-6	5 mL
12	47	Ethynyl-4-fluorobenzene, 1-	47.8	120.13	1.048	Aldrich	40,433-0	500 mg
13	48	Ethynyl-9-fluorenol, 9-	86.0	206.25	1.000	GFS	143705	10 g
14	17	Ethynylcyclohexene, 1-	49.0	106.17	0.903	Aldrich	31,657-1	5 g
15	49	Ethynylcyclopentanol, 1-	47.8	110.16	0.962	Aldrich	13,086-9	5 g
16	18	Ethynylestradiol 3-methyl ether	129.5	310.44	1.000	Aldrich	85,587-1	5 g
17	19	Ethynylpyridine, 2-	45.7	103.12	0.940	GFS	143907	1 g
18	20	Ethynyltoluene, 4-	52.9	116.16	0.916	Aldrich	20,650-4	5 g
19	22	Hexyne, 1-	47.9	82.15	0.715	Aldrich	24,442-2	25 mL
20	23	Hexynenitrile, 5-	43.7	93.13	0.889	Aldrich	27,134-9	5 g
21	24	Methyl propargyl ether	35.2	70.09	0.830	Aldrich	17,719-9	10 g
22	25	Methyl-1-buten-3-yne, 2-	39.7	66.10	0.695	Aldrich	M3,280-1	5 g
23	*	Methyl-3-butyn-2-ol, 2-	40.4	84.12	0.868	Aldrich	12,976-3	5 mL
24	26	Methyl-N-propargylbenzylamine, N-	70.3	159.23	0.944	Aldrich	M7,425-3	5 g
25	*27*	*Nonadiyne, 1,8-*	*156.6*	*120.20*	*0.799*	*Aldrich*	*16,130-6*	*10 g*
26	28	Pentyne, 1-	41.1	68.12	0.691	Aldrich	25,656-0	5 g
27	29	Phenyl-1-butyne, 4-	58.6	130.19	0.926	GFS	184701	5 g
28	30	Phenyl-1-propyne, 3-	51.9	116.16	0.934	Aldrich	37,684-1	5 g
29	31	Phenylacetylene	45.8	102.14	0.930	Aldrich	11,770-6	25 mL
30	37,53	Propiolaldehyde diethyl acetal	59.2	128.17	0.894	Aldrich	30,360-7	5 g
31		SKIP CODON	0.0	127.90	-			
			AVERAGE	*123.85*				

BB#	Test #	Chemical Name	2-pyr	mg or uL req'd	uL DIPEA	MW	d	salt mult		Aldrich Catalog #	Size
Table I.		**Amine building blocks used in library synthesis.**									
		beta-branched or greater (mult=1)	245.43	umol amine (25 eq)							
		alpha-branched (mult = 2)	490.86	umol amine (50 eq)							
		2-hydroxypyridine (2-pyr) stock solutions	1.0	49.09 umol (5 eq) in THF							
			1.1	49.09 umol (5 eq) in 3:2 CH2Cl2/DMF							
			2.0	98.17 umol (10 eq) in THF							
1	1	Allylamine	1.0	18.4		57.10	0.761	1		24,107-5	50 mL
2	5	Aminoacetaldehyde diethyl acetal	1.0	35.7		133.19	0.916	1		A3,720-0	25 mL
3	6	Aminoacetaldehyde dimethyl acetal	1.0	26.7		105.14	0.965	1		12,196-7	25 mL
4	8	Aminoethyl)benzenesulfonamide, 4-(2-	1.0	49.1		200.26	1.000	1		27,524-7	25 g
5	9	Aminoethyl)morpholine, 4-(2-	1.0	32.2		130.19	0.992	1		A5,500-4	5 g
6	78	Aminoethyl)pyridine, 2-(2-	1.0	29.3		122.17	1.021	1		A5,530-6	10 g
7	11	Aminoethyl)pyrrolidine, 1-(2-	1.0	31.1		114.19	0.901	1		A5,535-7	5 g
8	13	Aminoindan, (R)-(-)-1-	2.0	63.0		133.19	1.038	2		44,534-7	1 g
9	14	Aminoindan, (S)-(+)-1-	2.0	63.0		133.19	1.038	2		44,535-5	1 g
10	±15	Aminomethyl)-15-crown-5, 2-(	1.0	54.0		249.31	1.134	1		38,841-6	1 g
11	17	Aminomethyl)cyclopropane, (	1.0	21.3		71.12	0.820	1		35,952-1	1 mL
12	10'	Aminomethyl)pyridine, 2-(	1.0	25.0		108.14	1.062	1		A6,540-9	5 g
13	19,79	Aminomethyl)pyridine, 3-(	1.0	25.0		108.14	1.062	1		A6,540-9	5 g
14	20	Aminomethyl)pyridine, 4-(	1.0	23.9		108.14	1.065	1		A6,560-3	25 g
15	23	Aminopropyl)imidazole, 1-(3-	1.0	29.3		125.18	1.049	1		27,226-4	50 g
16	24	Aminopropyltrimethoxysilane, 3-	1.0	42.3		179.29	1.027	1		28,177-8	5 mL
17	28	Benzylamine	1.0	25.3		107.16	0.981	1		18,570-1	5 g
18	30	Bornylamine, (R)-(+)-	2.0	75.2		153.27	1.000	2		35,993-9	500 mg
19	31	Butylamine	1.0	21.3		73.14	0.740	1		23,991-7	50 g
20	80	Butylamine, (R)-(-)-sec-	2.0	49.1		73.14	0.731	2		29,664-3	1 g
21	81	Butylamine, (S)-(+)-sec-	2.0	49.1		73.14	0.731	2		29,665-1	1 g
22	32	Cyclobutylamine	2.0	41.9		71.12	0.833	2		25,518-5	1 g
23	34	Cyclohexylamine	2.0	56.2		99.18	0.867	2		24,064-8	5 mL
24	82	Cyclohexylethylamine, (R)-(-)-1-	2.0	73.0		127.33	0.856	2		33,650-5	5 g
25	83	Cyclohexylethylamine, (S)-(+)-1-	2.0	73.0		127.33	0.856	2		33,651-3	5 g
26	35	Cyclopentylamine	2.0	48.4		85.15	0.863	2		C11,500-2	5 g
27	36	Cyclopropylamine	2.0	34.0		57.10	0.824	2		12,550-4	10 g
28	38	Diethoxymethylsilyl)propylamine, 3-(	1.0	51.3		191.35	0.916	1		37,189-0	50 mL
29	39	Dimethoxyphenethylamine, 3,4-	1.0	41.4		181.24	1.074	1		D13,620-4	25 g
30	41	Dimethylaminopropylamine, 3-	1.0	30.9		102.18	0.812	1		24,005-2	50 mL
31	43	Ethylamine (2.0M in THF)	1.0	122.7		500.00	1.000	1		39,507-2	100 mL
32	49'	Fluorobenzylamine, 3-	1.0	28.0		125.15	1.097	1			
33	46	Fluorophenethylamine, 4-	1.0	32.2		139.17	1.061	1		36,182-8	10 g
34	48	Geranylamine	1.0	45.4		153.27	0.829	1		41,264-3	5 g
35	50	Isopinocampheylamine, (1R,2R,3R,5S)-(-)-	2.0	82.8		153.27	0.909	2		39,165-4	5 g

Table I.	Amine building blocks used in library synthesis.										
	Test			mg or uL	uL				salt	Aldrich	
BB#	#	Chemical Name	2-pyr	req'd	DIPEA	MW	d	mult		Catalog #	Size
36	51	Isopinocampheylamine,	2.0	32.3		153.27	0.909	2		39,166-2	5g
		(1S,2S,3S,5R)-(+)-									
37	52	Isopropylamine	2.0	41.3		59.11	0.694	2		10,906-1	25 mL
38	53	Methoxybenzylamine, 2-	1.0	32.0		137.18	1.051	1		15,988-3	5 g
39	54	Methoxybenzylamine, 4-	1.0	32.1		137.18	1.050	1		M1,110-3	25 g
40	55	Methoxyethylamine, 2-	1.0	21.8		75.11	0.864	1		24,106-7	50 mL
41	56	Methoxyphenethylamine, 2-	1.0	35.9		151.21	1.033	1		37,359-1	5 g
42	57	Methoxyphenethylamine, 3-	1.0	35.8		151.21	1.038	1		27,022-9	5 g
43	58	Methoxyphenethylamine, 4-	1.0	35.9		151.21	1.033	1		18,730-5	5 g
44	59	Methoxypropylamine, 3-	1.0	25.0		89.14	0.874	1		M2,500-7	25 mL
45	60	Methylamine (2.0M in THF)	1.0	122.7		500.00	1.000	1		39,505-6	100 mL
46	85	Methylbenzylamine, (R)-(+)-a-	2.0	63.3		121.18	0.940	2		42,193-6	5 mL
47	61	Myrtanylamine, (-)-cis-	1.0	31.1		153.27	0.915	1		18,080-7	10 g
48	86	Napthyl)ethylamine, (S)-(-)-1-(1-	2.0	79.3		171.25	1.060	2		27,745-0	5 g
49	62	Napthylenemethylamine, 1-	1.0	35.0		157.22	1.073	1		12,703-5	5 g
50	63	Nitrobenzylamine hydrochloride, 3-	1.1	35.3	35.5	188.62	1.000	1	1	19,166-3	5 g
51	65	Octylamine	1.0	40.6		129.25	0.782	1		O-580-2	100 g
52	66	Phenethylamine	1.0	30.3		121.18	0.965	1		40,726-7	100 mL
53	69	Piperonylamine	1.0	30.6		151.17	1.214	1		P4,950-3	25 g
54	70	Propargyl amine	1.0	16.8		55.08	0.803	1		P5,090-0	5 g
55	71	Tetrahydrofurfurylamine, (R)-(-)-	1.0	25.8		101.15	0.980	1		41,293-7	1 g
56	72	Tetrahydrofurfurylamine, (S)-(+)-	1.0	25.8		101.15	0.980	1		41,294-5	1 g
57	73	Tetramethyl-1,3-propanediamine,	1.0	39.1		130.24	0.818	1		22,741-2	25 g
		N,N,2,2-									
58	74	Thiopheneethylamine, 2-	1.0	28.7		127.21	1.087	1		42,327-0	5 g
59	87	Trifluoromethoxy)benzylamine, 4-(	1.0	37.5		191.15	1.252	1		34,098-7	1 g
60	88	Trifluoromethyl)benzylamine, 3-(	1.0	33.2		175.16	1.222	1		26,349-4	5 g
61	76	Tryptamine	1.0	39.3		160.22	1.000	1		19,374-7	10 g
62	77	Veratrylamine	1.0	37.0		167.21	1.109	1		V130-9	5 g
63		SKIP CODON				-	-				
					AVERAGE	*139.95*					

Table J.		Acid building blocks used in library synthesis.					
		carboxylic acid 871.77 umol (2 x 50 eq)					
	Test		mg or uL			Aldrich	
BB#	#	Chemical Name	acid	MW	d	Catalog #	Size
1	1	Acetic acid	49.9	60.05	1.049	33,882-6	25 mL
2	85	Acetoxyacetic acid	102.9	118.09	1.000	30,234-1	5 g
3	5	Anisic acid, m-	132.5	152.15	1.000	11,771-4	25 g
4	86	Benzofurancarboxylic acid, 2-	141.3	162.14	1.000	30,727-0	5 g
5	8	Benzoic acid	106.5	122.12	1.000	24,238-1	25 g
6	9	Butynoic acid, 2-	73.3	84.07	1.000	30,366-6	5 g
7	11	Chloropropionic acid, 3-	94.6	108.52	1.000	13,269-1	5 g
8	87	Cinnoline-4-carboyxlic acid	151.8	174.16	1.000	C8,215-9	1 g
9	12	Crotonic acid	75.1	86.09	1.000	23,956-9	50 g
10	14	Cyanobenzoic acid, 3-	128.3	147.13	1.000	15,716-3	1 g
11	15	Cyanobenzoic acid, 4-	128.3	147.13	1.000	C8,980-3	5 g
12	16	Cyclohexanecarboxylic acid	108.2	128.17	1.033	10,183-4	5 g
13	17	Cyclopentanecarboxylic acid	94.5	114.14	1.053	C11,200-3	5 g
14	18	Cyclopentylacetic acid	109.3	128.17	1.022	12,549-0	5 g
15	19	Cyclopropanecarboxylic acid	69.0	86.09	1.088	C11,660-2	25 g
16	20	Dihydro-2,2-dimethyl-4-oxo-2H-	148.3	170.16	1.000	19,572-3	5 g
		pyran-6-carboxylic acid, 3,4-					
17	21	Dihydro-2-methylbenzoic acid, 1,4-	120.5	138.17	1.000	30,035-7	5 g
18	89	Dimethylacrylic acid, 3,3-	87.3	100.12	1.000	D13,860-6	5 g
19	25	Ferroceneacetic acid	212.8	244.08	1.000	33,504-5	500 mg
20	27	Furanacrylic acid, trans-3-	120.4	138.12	1.000	33,638-6	5 g
21	28	Furoic acid, 2-	97.7	112.08	1.000	F2,050-5	5 g
22	29	Furoic acid, 3-	97.7	112.08	1.000	16,339-2	5 g
23	31	Hexadienoic acid, 2,4- (Sorbic acid)	97.8	112.13	1.000	24,010-9	50 g
24	32	Isobutyric acid	80.9	88.11	0.950	24,016-8	50 mL
25	33	Isonicotinic acid	107.3	123.11	1.000	I-1,750-8	5 g
26	34	Isovaleric acid	95.0	102.13	0.937	12,954-2	5 mL
27	35	Levulinic acid	89.3	116.12	1.134	L200-9	50 g
28	36	Linolenic acid	265.5	278.44	0.914	85,601-0	5 g
29	37	Menthoxyacetic acid, (+)-	183.2	214.31	1.020	44,869-7	5 mL
30	38	Menthoxyacetic acid, (-)-	183.2	214.31	1.020	M300-0	10 g
31	39	Methacrylic acid	73.9	86.09	1.015	39,537-4	5 mL
32	91	Methoxy-1-indanone-3-acetic acid, 5-	192.0	220.23	1.000	22,528-2	1 g
33	40	Methoxyacetic acid	66.9	90.08	1.174	19,455-7	50 g
34	41	Methoxyphenylacetic acid, (R)-(-)-a-	144.9	166.18	1.000	24,896-7	1 g
35	43	Methoxyphenylacetic acid, 2-	144.9	166.18	1.000	18,065-3	5 g
36	44	Methoxyphenylacetic acid, 3-	144.9	166.18	1.000	M1,900-7	5 g
37	45	Methoxyphenylacetic acid, 4-	144.9	166.18	1.000	M1,920-1	5 g
38	46	Methyl (1S,2R)-(+)-cis-1,2,3,6-	160.6	184.19	1.000	36,728-1	1 g
		tetrahydrophthalate, 1-					
39	47	Methyl glutarate, mono-	111.9	146.14	1.139	M4,735-3	5 g
40	48	Methyl phthalate, mono-	157.1	180.16	1.000	31,764-0	25 g
41	49	Methyl terephthalate, mono-	157.1	180.16	1.000	32,838-3	5 g
42	92	Methyl-2-pyrrolecarboxylic acid, 1-	109.1	125.13	1.000	15,314-1	5 g

Table J.		Acid building blocks used in library synthesis.					
	Test		mg or uL			Aldrich	
BB#	#	Chemical Name	acid	MW	d	Catalog #	Size
43	53	Methylenedioxy)phenylacetic acid, 3,4-(	157.1	180.16	1.000	32,967-3	5 g
44	54	Methylindole-2-carboxylic acid, 1-	152.7	175.19	1.000	13,415-5	5 g
45	55	Nicotinic acid	107.3	123.11	1.000	N785-0	5 g
46	60	Norbornaneacetic acid, 2-	126.2	154.21	1.065	12,726-4	5 g
47	62	Oxo-4-phenyl-3-oxazolidineacetic acid, (S)-(+)-2-	192.8	221.21	1.000	39,134-4	1 g
48	63	Oxotricyclo[2.2.1.0(2,6)]heptane-7-carboxylic acid,	132.6	152.15	1.000	32,285-7	1 g
		anti-3-					
49	64	Phenylacetic acid	109.8	136.15	1.081	P1,662-1	5 g
50	67	Picolinic acid	107.3	123.11	1.000	P4,280-0	5 g
51	68	Propionic acid	55.0	74.08	0.993	40,290-7	100 mL
52	69	Pyrazinecarboxylic acid, 2-	108.2	124.10	1.000	P5,610-0	25 g
53	94	Pyridyl)acrylic acid, trans-3-(3-	130.0	149.15	1.000	P6,620-3	5 g
54	±75	Tetrahydro-2-furoic acid	88.7	116.12	1.209	34,151-7	5 g
55	±76	Tetrahydro-3-furoic acid	83.4	116.12	1.214	33,995-4	5 g
56	95	Thienyl)acrylic acid, 3-(2-	134.4	154.19	1.000	13,058-3	5 g
57	80	Thiophenecarboxylic acid, 2-	111.7	128.15	1.000	T3,280-3	25 g
58	81	Thiophenecarboxylic acid, 3-	111.7	128.15	1.000	24,776-6	5 g
59	96	Trifluoro-m-toluic acid, a,a,a-	165.7	190.12	1.000	18,834-4	5 g
60	97	Trifluoro-o-toluic acid,. a,a,a-	165.7	190.12	1.000	19,688-6	5 g
61	98	Trifluoro-p-toluic acid, a,a,a-	165.7	190.12	1.000	19,689-4	5 g
62	84	Vinylacetic acid	74.4	86.09	1.013	13,471-6	25 g
63		SKIP CODON	>	-	-	-	-
		AVERAGE	*123.32*	*143.07*			

Table K.	Binary encoding scheme for diazoketone tags.																						
	Note that tags 5B, 6B, and 7B were not used.																						
Building	Spacer		Epoxyol		Nitrone		Alkyne					Amine						Acid					
Block #	1C	2C	1B	1D	2B	2D	3B	3D	4B	4D	5D	6D	7D	8B	8D	9B	9D	10B	10D	7A	8A	9A	10A
1	0	1	0	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1
2	1	0	1	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0
3	1	1			1	1	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	1	1
4							0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
5							0	0	1	0	1	0	0	0	1	0	1	0	0	0	1	0	1
6							0	0	1	1	0	0	0	0	1	1	0	0	0	0	1	1	0
7							0	0	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1
8							0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0
9							0	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
10							0	1	0	1	0	0	0	1	0	1	0	0	0	1	0	1	0
11							0	1	0	1	1	0	0	1	0	1	1	0	0	1	0	1	1
12							0	1	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0
13							0	1	1	0	1	0	0	1	1	0	1	0	0	1	1	0	1
14							0	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0
15							0	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1
16							1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0
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19							1	0	0	1	1	0	1	0	0	1	1	0	1	0	0	1	1
20							1	0	1	0	0	0	1	0	1	0	0	0	1	0	1	0	0
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22							1	0	1	1	0	0	1	0	1	1	0	0	1	0	1	1	0
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24							1	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0
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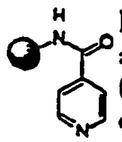
26							1	1	0	1	0	0	1	1	0	1	0	0	1	1	0	1	0
27							1	1	0	1	1	0	1	1	0	1	1	0	1	1	0	1	1
28							1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0	0
29							1	1	1	0	1	0	1	1	1	0	1	0	1	1	1	0	1
30							1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	0
31							1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1

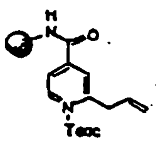
Appendix B: Isoquinuclidine Based Syntheses

Experimental Section

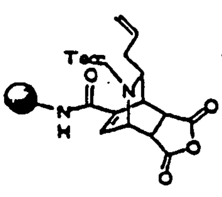
General Methods. All reactions were performed on Tentagel polystyrene resin purchased from Rapp Polymere, Germany. In addition to standard polyethylene glycol spacers, the resin was charged with a ph tocleavable linker element. Cleavage f compounds from solid phase at any step of synthesis was carried out by placing resin in a minimal amount of acetonitrile followed by exposure to UV (300nm??) for approximately 1hr. All reactions were carried out at room temperature unless otherwise noted.



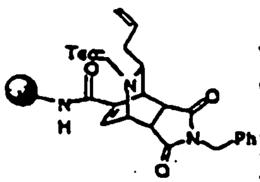
Isonicotinamide. 1g Tentagel resin (0.24 mmol/g) was placed in a 10mL reaction barrel and allowed to swell in dry CH_2Cl_2. Isonicotinoyl chloride hydrochloride was added (213.61mg, 5eq) and the resulting suspension mixed well. Freshly distilled diisopropylethylamine was slowly added (0.641mL, 15eq) resulting in dissolution of any remaining insoluble acid chloride. The reaction was shaken and allowed to proceed for 15 min, after which the resin was drained of reactants and washed well with CH_2Cl_2, THF, and iPrOH 3 times. The resin was given a final wash with trimethylorthoformate (TMOF) followed by anhydrous THF, and dried under a nitrogen stream. ^1H NMR: δ 8.77 (dd, J = 4.46, 1.68 Hz, 2H), 7.65 (dd, J = 4.42, 1.72, 2H), 6.08(d, J = 107 Hz, 2H); ^{13}C NMR: δ 167.22, 150.73, 140.43, 121.07; IR (NaCl plate): 3327.6, 3059.4, 1682.1, 1622.3 cm^{-1}.



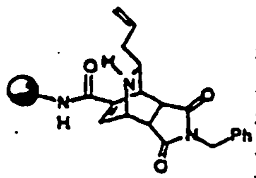
1g resin (approx 0.24 mmol/g) was swelled with dry CH_2Cl_2 in a 10mL reaction barrel. Allyltributyltin was added (1.86mL, 25eq) and the resulting solution shaken well and cooled to 0°C. Teoc-Cl (trimethylsilylethoxycarbonyl chloride) was then added (1.08mL, 25eq), the reaction barrel vented, and shaken for 6 hours, warming to room temperature after the first hour. The reaction vessel was then drained and the resin washed with alternating solutions of anhydrous hexane and CH_2Cl_2 (10 times) to remove all residual tin. Subsequent washes were carried out using CH_2Cl_2, THF, DMF, MeCN, and iPrOH (3x). The final wash of TMOF followed by THF dried the resin, which was stored under N_2. The product generated in this step is vulnerable to UV-induced photorearrangement; the data shown below pertain to desired product only. ^1H NMR: δ 6.90, 6.78 (d, J = 15.5Hz), 6.22 (m), 5.95 - 5.55 (m), 5.09, 5.01, 4.95 (m), 4.45, 4.40 (m), 2.35 (dm), 1.05 (m), 0.05. HPLC ret. (reverse phase): 2.488min. MS: M^+ = 309.



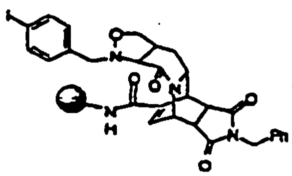
1g resin (approx. 0.24 mmol/g) was placed dry into a 20mL screw top glass vial. Anhydrous toluene (8mL) was then added, and the solution shaken to disperse the resin uniformly. 3 eq maleic anhydride (70mg) were dissolved in a minimal amount of anhydrous acetonitrile, and added to the resin. The vial threads were sealed with telfon tape, the reaction heated to 80°C for 12hr, and the vessel shaken well every 3 hours. The resin was filtered into a fritted reaction vessel and the glass vial washed with CH_2Cl_2 to remove any adherent beads. The resin was washed 3x with CH_2Cl_2, THF, DMF, MeCN, and iPrOH. TMOF and THF solutions were used to dry the resin, which was stored under N_2. ^1H NMR: δ 7.15, 7.05 (d), 6.31, 5.79 (m), 5.49, 5.37 (t), 5.17 - 5.05 (m), 4.26 (m), 3.91, 3.31 (dd), 3.21, 3.11, 2.59, 2.49, 1.86 (m), 1.69, 1.39, 1.05 (m), 0.07. HPLC ret. (reverse phase): 2.224min. MS: M^+ = 407.



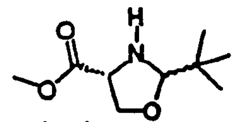
1g resin (approx. 0.24 mmol/g) was placed dry into a 20mL screw top glass vial. Anhydrous toluene (8mL) was then added, and the solution shaken to disperse the resin uniformly. 5 eq benzylamine (0.131mL) was then added to the resin. The vial threads were sealed with telfon tape, the reaction heated to 80°C for 12hr, and the vessel shaken well every 3 hours. The resin was filtered into a fritted reaction vessel and the glass vial washed with CH_2Cl_2 to remove any adherent beads. The resin was washed 3x with CH_2Cl_2, THF, DMF, MeCN, and iPrOH. TMOF and THF solutions were used to dry the resin, which was stored under N_2. HPLC ret. (reverse phase): 2.545min. MS: $M^+ + Na = 518$



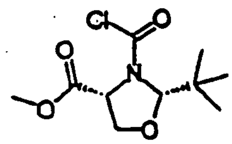
1g resin (approx. 0.24 mmol/g) was swelled with CH_2Cl_2 in a 10mL reaction vessel. The resin was drained and CH_2Cl_2 sufficient to cover the resin added. Approximately 2mL TFA was added, the reaction vessel shaken, and vented. Shaking was continued for 10min, after which the solution was drained, and the TFA treatment repeated for 15min. The resin was drained, fresh CH_2Cl_2 added, and approximately 1mL DIPEA (diisopropylethylamine) added to neutralize any residual TFA. The resin was washed with CH_2Cl_2, THF, DMF, MeCN, and iPrOH (3 times). TMOF and THF solutions were used to dry the resin, which was stored under N_2. ^1H NMR: δ 7.35 (m), 7.13 (d), 6.80 (d), 6.05 (m), 5.75 (m), 5.65 (m), 5.03 (m), 4.7 - 4.4 (m), 4.45 (d), 3.6 (d), 3.25 (dd), 3.11 (td), 3.08 (dd), 2.80 (m), 1.90 (m), 1.79 (dm), 1.37 (m). HPLC ret. (reverse phase): 1.808min. MS: $M^+ = 352$



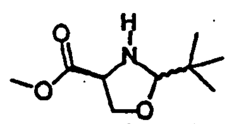
1g resin (approx. 0.24 mmol/g) was swelled with 7mL CH_2Cl_2 in a 10mL reaction vessel. 25 eq *p*-iodobenzylnitrone (1.82g) was added and the vessel shaken to dissolve the solid material. 25 eq PyBroP (2.79g) was then added, and the mixture shaken again. Upon dissolution of all solid reagents, the vessel was cooled to -20°C. DIPEA was then added (40eq, 1.7mL) and the reaction mixture shaken at -20°C for 6hr. Subsequent washing was performed 3x with CH_2Cl_2, THF, DMF, MeCN, and iPrOH. TMOF and THF solutions were used to dry the resin, which was then stored under N_2. ^1H NMR: δ 7.91 (d), 7.54 (d), 7.30 (m), 7.02 (t), 6.53 (dd), 5.75 (dd), 5.09 (t), 4.60 (t), 4.47 (d), 4.07 (t), 3.81, 3.76 (m), 3.65 (d), 3.4 - 3.3 (m), 3.14, 1.95 (m), 1.78. HPLC ret. (reverse phase): 2.182min. MS: $M^+ = 639$.



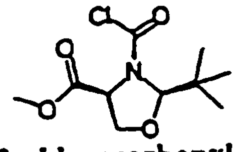
Methyl (4R)-2-(t-butyl)-3-(1,3)-oxazolidine-4-carboxylate. (Dieter Seebach and Johannes D. Aebi, *Teterahedron Letters*, Vol. 25, No. 24, pp 2545-2548) To a 100 mL round-bottomed flask equipped with stir bar and Dean Stark trap and purged with N_2 was added D-serine methyl ester hydrochloride (6.2g, 40 mmol, 1eq) followed by n-pentane (50 mL). Pivaldehyde (8.8 mL, 80 mmol, 2eq) was added to the mixture followed by triethylamine (6.1 mL, 44 mmol, 1.1 eq). The mixture was heated to reflux for 16h with removal of water. The mixture was cooled to 23°C, filtered, washed with ether (50 mL) and concentrated to an oil which was used without further purification in the next step.



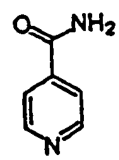
Methyl (2S,4R)-2-(t-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate. Jaques Streith, Arnaud Boiron, Thierry Sifferlen, Christiane Strehler, Theophile Tschamber *Tetrahedron Letters*, Vol. 35, No. 23, pp. 3927-3930). To a stirred solution of oxazolidine (7.02g, 37.5 mmol, 1 eq) in CH_2Cl_2 (141ml) at -15°C was added a 1.93M solution of phosgene in toluene (29 mL, 56 mmol, 1.5 eq) dropwise. Triethyl amine (6.7 mL, 48 mmol, 1.3 eq) was added dropwise and the reaction was allowed to warm to 23°C. After 2h N_2 was bubled through the reaction mixture in order to remove excess phosgene. The solvents were evaporated and the residue was slurried with AcOEt/cyclohexane (3:7) and the mixture was filtered. The filtrate was concentrated and purified by flash chromatography (rf=). Recrystallisation from pentane yielded Methyl (2S,4R)-2-(t-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate (7.9g, 85%), m.p.= 78°C. NMR (400 MHz, $CDCl_3$): δ 5.17 (s, 1H, C2-H), 4.89 (dd, 1H, J= 7.9, 4.8, C4-H), 4.39 (dd, 1H, J= 8.8, 4.5, C5-H_β), 4.22 (dd, 1H, J= 8.8, 8.1, C5-H_α), 3.81 (s, 3H, CO_2CH_3), 0.97 (s, 9H, $C(CH_3)_3$).



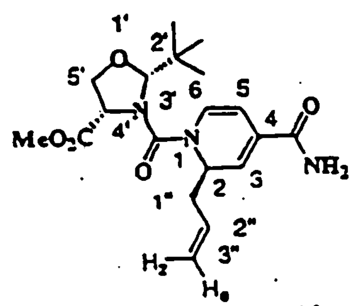
Methyl (4S)-2-(t-butyl)-3-(1,3)-oxazolidine-4-carboxylate. (Dieter Seebach and Johannes D. Aebi, *Teterahedron Letters*, Vol. 25, No. 24, pp 2545-2548) To a 100 mL round-bottomed flask equipped with stir bar and Dean Stark trap and purged with N_2 was added L-serine methyl ester hydrochloride (6.2g, 40 mmol, 1eq) followed by n-pentane (50 mL). Pivaldehyde (8.8 mL, 80 mmol, 2eq) was added to the mixture followed by triethylamine (6.1 mL, 44 mmol, 1.1 eq). The mixture was heated to reflux for 16h with removal of water. The mixture was cooled to 23°C, filtered, washed with ether (50 mL) and concentrated to an oil which was used without further purification in the next step.



Methyl (2R,4S)-2-(t-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate. (Jaques Streith, Arnaud Boiron, Thierry Sifferlen, Christiane Strehler, Theophile Tschamber *tetrahedron Letters*, Vol. 35, No. 23, pp. 3927-3930). To a stirred solution of oxazolidine (7.02g, 37.5 mmol, 1 eq) in CH_2Cl_2 (141ml) at -15°C was added a 1.93M solution of phosgene in toluene (29 mL, 56 mmol, 1.5 eq) dropwise. Triethyl amine (6.7 mL, 48 mmol, 1.3 eq) was added dropwise and the reaction was allowed to warm to 23°C. After 2h N_2 was bubled through the reaction mixture in order to remove excess phosgene. The solvents were evaporated and the residue was slurried with AcOEt/ cyclohexane (3:7) and the mixture was filtered. The filtrate was concentrated and purified by flash chromatography (rf=). Recrystallisation from pentane yielded Methyl (2R,4S)-2-(t-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate (7.9g, 85%), m.p.= 78°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.17 (s, 1H, C2-H), 4.89 (dd, 1H, J= 7.9, 4.8, C4-H), 4.39 (dd, 1H, J= 8.8, 4.5, C5-H_β), 4.22 (dd, 1H, J= 8.8, 8.1, C5-H_α), 3.81 (s, 3H, CO_2CH_3), 0.97 (s, 9H, $C(CH_3)_3$).

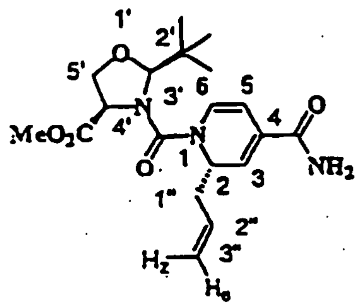


Isonicotinamide. 3-Amino-3-(2'-nitrophenyl)-2,2-dimethylproponylcarboxamide-Tentagel resin (200 mg, 0.27 meq/g, 54 μmol, 1 eq) was placed in a PD-10 column. Isonicotinoylchloride hydrochloride (48 mg, 270 μmol, 5 eq), distilled CH_2Cl_2 (2.4 mL), and DIPEA (141 μl, 810 μmol, 15 eq) were added in sequence. After 1h, the resin was washed 3 x DMF, 3 x IPA, 3 x DMF, 3 x CH_2Cl_2, 3 x DMF, 3 x CH_3CN, 3 x THF, 3 x CH_2Cl_2 to yield isonicotinoyl-3-Amino-3-(2'-nitrophenyl)-2,2-dimethylproponylcarboxamide-Tentagel resin which was negative to Kaiser ninhydrin test. Photolysis of the resin yielded the crude isonicotinamide, as a yellow oil. IR (NaCl) 3175, 1684, 1554, 1506, 1412, 612 cm^{-1}. ^{1}H-NMR (500 MHz, CD_3CN): δ 8.70 (br m, 2H), 7.65 (dd, J = 4.4, 1.7, 2H). EI-MS (Direct) m/z (rel int): 122 (M], 100), 106 (33).



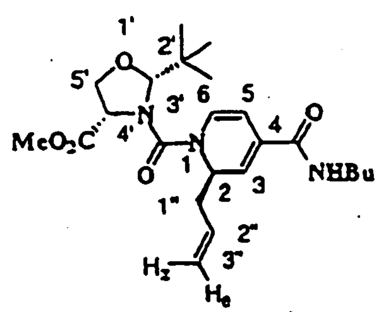
Methyl (2R,2'R, 4'S)-3'-[2-allyl-4-carboxamide-1,2-dihydro-1-pryidinyl]-carbonyl-2'-t-butyl-(1,3)-oxazoline-4-carboxylate. Isonicotinamide resin (80

mg, 0.27 meq/g, 21.6 μmol, 1eq) was placed in a new PD-10 column along with methyl (2R,4S)-2-(t-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate (54 mg, 216 μmol, 10 eq), NaI (65 mg, 432 μmol, 20 eq) and toluene (800 μl). The mixture was agitated by 360° rotation for 5 days during which time the resin changed colors from tan to burgundy. the resin was filtered and washed with toluene 10 x 1 mL, resuspended in toluene (900 μL), cooled to 0°C and treated with allyltributyltin (860 μl, 2.8 mmol, 130 eq). The mixture was agitated by 360° rotation for 1 day. The resin washed with hexanes 50 x 1 mL, CH_2Cl_2 50 x 1 mL.



Methyl (2S,2'S, 4'R)-3'-[2-allyl-4-carboxamide-1,2-dihydro-1-pryidinyl]-carbonyl-2'-t-butyl-(1,3)-oxazoline-4-carboxylate. Isonicotinamide resin (80 mg, 0.27 meq/g, 21.6 μmol, 1eq) was placed in a new PD-10 column along with methyl (2S,4R)-2-(t-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate (54 mg, 216 μmol, 10 eq), NaI (65 mg, 432 μmol, 20 eq) and toluene (800 μl). The mixture was agitated by 360° rotation for 5 days during which time the resin changed colors from tan to burgundy. the resin was filtered and washed with toluene 10 x 1 mL, resuspended in toluene (900 μL), cooled to 0°C and treated with allyltributyltin (860 μl, 2.8 mmol, 130 eq). The mixture was agitated by 360° rotation for 1 day. The resin washed with hexanes 50 x 1 mL, CH_2Cl_2 50 x 1 mL.

Solution Phase Studies



Methyl (2R,2'R, 4'S)-3'-[2-allyl-4-butylcarboxamide-1,2-dihydro-1-pryidinyl]-carbonyl-2'-t-butyl-(1,3)-oxazoline-4-carboxylate. To a flame dried 5 mL round-bottomed flask equipped with stir bar and purged with N_2 was added N-butyl isonicotinamide (50 mg, 280μmol, 1eq), Methyl (2R,4S)-2-(t-butyl)-3-chlorocarbonyl-(1,3)-oxazolidine-4-carboxylate (70 mg, 280 μmol, 1 eq), NaI (84 mg, 560 μmol, 2 eq) and toluene (1.2 mL). The flask was capped with a glass-stopper, sealed with parafilm and stirred for 5 days. The flask was then fitted with a nitrogen inlet and cooled to 0°C.

Allyltributyltin (86µl, 308 µmol, 1.1 eq) was added and the flask was allowed to warm to 23°C with stirring overnite. The mixture was filtered, concentrated and purified by column chromatography (SiO_2, 10% MeOH/$CHCl_3$) to afford 109 mg, 90% of Methyl (2R,2'R, 4'S)-3'-[2-allyl-4-butylcarboxamide-1,2-dihydro-1-pryidinyl] carbonyl-2'-t-butyl-(1,3)-oxazoline-4-carboxylate. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.99 (d, 1H, J= 7.6, C5-H), 6.17 (d, 1H, J= 6.2, C6-H), 5.8 (m, 1H, C1''-H), 5.72 (t, 1H, NH), 5.67 (dd, 1H, J= 7.6, 1.7, C3-H), 5.43 (s, 1H, C2'-H), 5.05 (m, 1H, C3''-H_t), 5.01 (brs, 1H, C3''-H_c), 4.74 (dd, 1H, J= , 6.3, C4'-H), 4.36 (d, 1H, J= 8.8, C5'-H_α), 4.09 (d, 1H, J= 6.03, C5'-H_β), 3.79 (m, 1H, C2-H), 3.75 (s, 3H, CO_2CH_3), 3.32 (m, 2H, $NHCH_2$), 2.4-2.3 (m, 2H, C1''-H), 1.4-1.2 (m, 4H, $(CH_2)_2$), 0.97 (s, 9H, C2'-t-Bu), 0.96 (t, 3H, CH_3).

Claims

What we claim is:

1. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

providing one or more template structures;

synthesizing one or more diversifiable scaffold structures containing reactive moieties and at least one stereocenter in one or more synthetic steps from said one or more template structures; and

diversifying said one or more scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

2. The method of claim 1, wherein said one or more isolated complex compounds comprises a library of isolated complex compounds containing at least 1,000,000 library members.

3. The method of claim 1, wherein said one or more isolated complex compounds comprises a library of isolated complex compounds containing at least 2,000,000 library members.

4. The method of claim 1, wherein said one or more diversifiable scaffold structures each contain at least four stereocenters and at least four diversifiable functionalities.

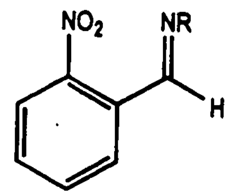
5. The method of claim 1, wherein providing said one or more template structures comprises synthesizing said one or more template structures in four steps or fewer and wherein said one or more diversifiable scaffold structures contain at least four stereocenters and at least four diversifiable functionalities.

6. The method of claim 1, further comprising attaching said one or more template structures to a solid support unit prior to the step of synthesizing said one or more diversifiable scaffold structures.

7. The method of claim 1, wherein providing said one or more template structures comprises synthesizing each of said one or more template structures directly on solid support units.

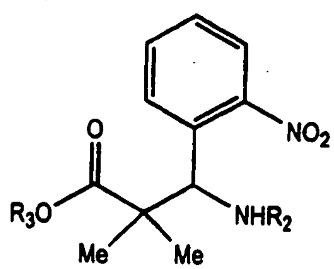
8. A method for generating a novel ortho-nitrobenzyl photolabile linker comprising:

(a) providing an imine having the following structure:



wherein R is a protecting group; and

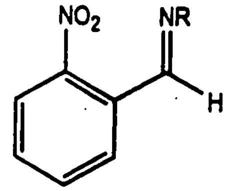
(b) forming an amino ester by the addition of the imine to the lithium enolate of methyl isobutyrate to generate a novel ortho-nitrobenzyl photolabile linker having the following structure:



wherein R_2 is selected from the group consisting of protecting group, spacer, isolated complex compound reminiscent of natural products, biomolecule, polymer and hydrogen; and R_3 is a solid support unit.

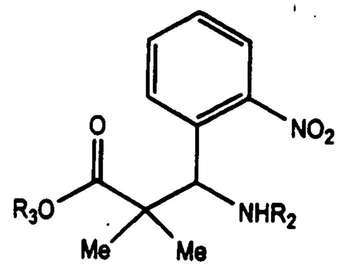
9. A method for generating a novel ortho-nitrobenzyl photolabile linker comprising:

(a) providing an imine having the following structure:



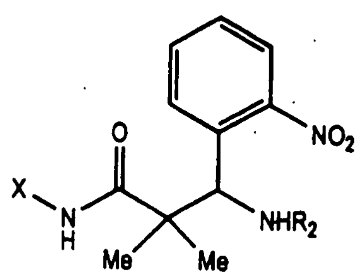
wherein R is a protecting group;

(b) forming an amino ester by addition of the imine to the lithium enolate of methyl isobutyrate to generate a compound having the following structure:



wherein R_2 is selected from the group consisting of protecting group, spacer, complex compound reminiscent of natural products, biomolecule, polymer and hydrogen; R_3 is a solid support unit; and

(c) saponifying the methyl ester to generate an acid which is subsequently reacted with an amine or amine containing moiety to generate a novel ortho-nitrobenzyl photolabile linker having the following structure:

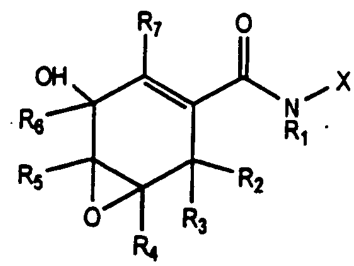


wherein R_2 is selected from the group consisting of protecting group, spacer, complex compound reminiscent of natural products, biomolecule, polymer and hydrogen; and X is a solid support unit.

10. The method of claim 9, further comprising reaction of said amino ester with a solid support to generate a novel solid support bound ortho-nitrobenzyl photolabile linker.

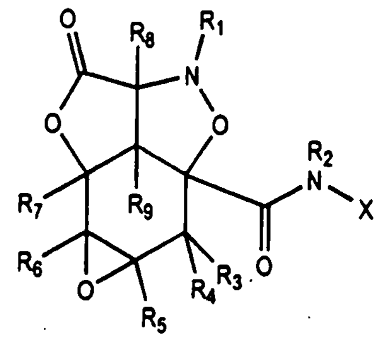
11. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:



wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

12. The method of claim 11, wherein synthesizing said epoxyol template comprises:
providing (-)-shikimic acid;
reaction of shikimic acid with DEAD and triphenylphosphine to yield an epoxide;
reaction of said epoxide with benzoic acid, triphenylphosphine and DEAD to yield the benzoate ester;
reaction of said benzoate ester with lithium hydroxide to yield one enantiomer of a carboxylic acid epoxyol template.

13. The method of claim 11, wherein synthesizing said epoxyol template comprises:
providing (-)-shikimic acid;
reaction of shikimic acid with acet xybutyrylbromide;

epoxidation with $NaOCH_3$ and subsequent Payne rearrangement;

reaction of said epoxide with lithium hydroxide to yield one enantiomer of a carboxylic acid epoxyol template.

14. The method of claim 11, further comprising attachment of said epoxyol template to the solid support unit.

15. A method for generating a library of isolated complex compounds reminiscent of natural products comprising:

(a) providing a collection of solid supports;

(b) reacting said collection of solid supports with one or more spacers and one or more skip codons to generate distinct solid support units;

(c) reacting each of said distinct solid support units with enantiomers of an epoxyol template to generate distinct solid support bound epoxyol templates;

(d) reacting each of said solid support bound epoxyol templates with one or more nitrones to generate tetracyclic templates;

(e) reacting each of said tetracyclic templates with one or more of a particular class of reagents and optionally one or more skip codons; and

(f) repeating step (e) for different classes of reagents until a desired library of natural product-like compounds is obtained.

16. The method of claim 15, wherein each of said tetracyclic templates is reacted sequentially with one or more terminal alkynes and optionally one or more skip codons; one or more amines and optionally one or more skip codons; and one or more acids and optionally one or more skip codons to generate a library of natural product-like compounds.

17. The method of claim 15 or 16, wherein each of said terminal alkynes is selected from the group consisting of acetaldehyde ethyl propargyl acetal, tert-butyl 1-methyl-2-propynyl ether, 4-(tert-butyl) phenylacetylene, tert-butyldimethylsilyl acetylene, 2-(3-butynloxy)tetrahydro-2H-pyran, 1-chloro-4-ethynylbenzene, 1,4-decadiyne (50% in hexane), 1,5-decadiyne, 3-dibutylamino-1-propyne, m-diethynylbenzene, 3,3-dimethyl-1-butyne, 1-dimethylamino-2-propyne, 1-dodecyne, ethyl ethynyl ether (50% in hexanes), ethynyl p-tolyl sulfone, 1-ethynyl-4-fluorobenzene, 1-ethynylcyclohexene, ethynylestradiol 3-methyl ether, 2-ethynylpyridine, 4-

ethynyltoluene, 1,5-hexadiyne (50% in hexane), 1-hexyne, 5-hexynenitrile, methyl propargyl ether, 2-methyl-1-buten-3-yne, methyl-N-propargylbenzylamine, 1,8-nonadiyne, 1-pentyne, 4-phenyl-1-butyne, 3-phenyl-1-propyne, phenylacetylene, propargyl ether, propargyn-1H-benzotriazole, N-(propargyloxy)phthalimide, N-propargylphthalimide, propargyltriphenylphosphonium bromide, proiolaldehyde diethyl acetal, tetrahydro-2-(2-propynyloxy)-2H-pyran, triethylsilylacetylene, tripropargylamine, 2-(3-butynloxy)tetrahydro-2H-pyran, 3,5-dimethyl-1-hexyn-3-ol, 1,1-diphenyl-2-propyn-1-ol, 1-ethynyl-1-cyclohexanol, 1-ethynyl-4-fluorobenzene, 9-ethynyl-9-fluorenol, 1-ethynylcyclopentanol, 1-heptyne, 3-methyl-1-pentyn-3-ol, 2-phenyl-3-butyn-2-ol, and propiolaldehyde diethyl acetal.

18. The method of claim 15 or 16, wherein each of said amines is selected from the group consisting of allylamine, 2-amino-1-propene-1,1,3-tricarbonitrile, 3-amino-1H-isoindole hydrochloride, 3-amino-5-methylisoxazole, aminoacetaldehyde diethyl acetal, aminoacetaldehyde dimethyl acetal, aminoacetonitrile bisulfate, 4-(2-aminoethyl)benzenesulfonamide, 4-(2-aminoethyl)morpholine, 2-(2-aminomethyl)pyridine, 1-(2-aminoethyl)pyrrolidine, 2-aminoindan hydroxchloride, (R)-(-)-1-aminoindan, (S)-(+)-1-aminoindan, 2-(aminomethyl)-15-crown-5, 4-(aminomethyl)benzenesulfonamide hydrochloride, (aminomethyl)cyclopropane, 2-pyrenemethylamine hydrochloride, 3-(aminomethyl)pyridine, 4-(aminomethyl)pyridine, 3-aminopropionitrile fumarate, 1-(3-aminopropyl)-2-pyrrolidinone, 1-(3-aminopropyl)imidazole, 3-aminopropyltrimethoxysilane, (R)-(+)-3-aminoquinuclidine dihydrochloride, (S)-(-)-3-aminoquinuclidine dihydrochloride, ammonia (0.5 M in dioxane), benzylamine, S-benzylcysteamine hydrochloride, (R)-(+)-bornylamine, butylamine, cyclobutylamine, cyclohexanemethylamine, cyclohexylamine, cyclopentylamine, cyclopropylamine, (R)-(+)-cycloserine, 3-(diethoxymethylsilyl)propylamine, 3,4-dimethoxyphenethylamine, 4-(dimethylamino)benzylamine dihydrochloride, 3-dimethylaminopropylamine, N,N-dimethylethylenediamine, ethylamine (2.0 M in THF), 1-ethylpropylamine, 2-fluoroethylamine hydrochloride, 4-fluorophenethylamine, furfurylamine, geranylamine, 3-fluorobenzylamine, (1R, 2R, 3R, 5S)-(-)-isopinocampheylamine, (1S, 2S, 3S, 5R)-(+)-isopinocampheylamine, isopropylamine, 2-methoxybenzylamine, 4-methoxybenzylamine, 2-methoxyethylamine, 2-methoxyphenethylamine, 3-methoxyphenethylamine, 4-methoxyphenethylamine, 3-methoxypropylamine, methylamine (2.0M in THF), (-)-cis-myrtanylamine, 1-napthylenemethylamine, 3-nitrobenzylamine hydrochloride, 4-nitrophenethylamine hydrochloride, octylamine, phenethylamine, trans-

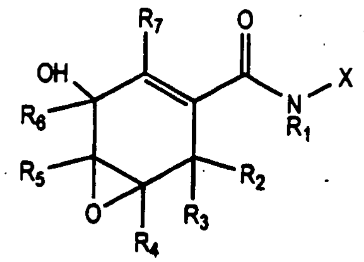
2phenylcyclopropylamine hydrochloride, 2-phenylglycinonitrile hydrochloride, piperonylamine, propargyl amine, (R)-(-)-tetrahydrofurfurylamine, (S)-(+)-tetrahydrofurfurylamine, N,N,2,2-tetramethyl-1,3-propanediamine, 2-thiopheneethylamine, 2,2,2-trifluoroethylamine, tryptamine, veratrylamine, 2-(2-aminoethyl)pyridine, 3-(aminomethyl)pyridine, (R)-(-)-sec-butylamine, (S)-(+)-sec-butylamine, (R)-(-)-1-cyclohexylethylamine, (S)-(+)-1-cyclohexylethylamine, isoamylamine, (R)-(+)-a-methylbenzylamine, (S)-(-)-1-(1-napthyl)ethylamine, 4-(trifluoromethyoxy)benzylamine, and 3-(trifluoromethyl)benzylamine.

19. The method of claim 15 or 16, wherein each of said sixty two acids is selected from the group consisting of acetic acid, 4-acetoxybenzoic acid, acetylsalicyclic acid, acrylic acid, m-anisic acid, o-anisic acid, p-anisic acid, benzoic acid, 2-butynoic acid, (3-carboxypropyl)trimethylammonium chloride, 3-chloropropionic acid, crotonic acid, cyanoacetic acid, 3-cyanobenzoic acid, 4-cyanobenzoic acid, cyclohexanecarboxylic acid, cyclopentanecarboxylic acid, cyclopentylacetic acid, cyclopropanecarboxylic acid, 3,4-dihydro-2,2-dimethyl-4-oxy-2H-pyran-6-carboxylic acid, 1,4-dihydro-2-methylbenzoic acid, 3-dimethylaminobenzoic acid, 4-dimethylaminobenzoic acid, N,N-dimethylglycine, ferroceneacetic acid, formic acid, trans-3-furanacrylic acid, 2-furoic acid, 3-furoic acid, furylacrylic acid, 2,4-hexadienoic acid (Sorbic acid), isobutyric acid, isonicotinic acid, isovaleric acid, levulinic acid, linolenic acid, (+)-menthoxyacetic acid, (-)-menthoxyacetic acid, methacrylic acid, methoxyacetic acid, (R)-(-)-a-methoxyphenylacetic acid, (S)-(+)-a-methoxyphenylacetic acid, 2-methoxyphenylacetic acid, 3-methoxyphenylacetic acid, 4-methoxyphenylacetic acid, 1-methyl (1S, 2R)-(+)-cis-1,2,3,6-tetrahydrophthalate, mono-methyl glutarate, mono-methyl phthalate, mono-methyl terephthalate, [1R-(1-α, 2b, 3a)]-(+)-3-methyl-2-(nitromethyl)-5-oxocyclopentaneacetic acid, 4-(3-methyl-5-oxo-2-pyrazolin-1-yl)benzoic acid, 6-methylchromone-2-carboxylic acid, 3,4-(methylenedioxy)phenylacetic acid, 1-methylindole-2-carboxylic acid, nicotinic acid, 5-nitro-2-furoic acid, 4-nitrobenzoic acid, 4-nitrophenylacetic acid, 3-nitropropionic acid, 2-norbornaneacetic acid, orotic acid monohydrate, (S)-(+)-2-oxo-4-phenyl-3-oxazolidineacetic acid, anti-3-oxotricyclo[2.2.1.0(2,6)]heptane-7-carboxylic acid, phenylacetic acid, phenylpropiolic acid, phthalylsulfathiazole, picolinic acid, propionic acid, 2-pyrazinecarboxylic acid, 2-pyridylacetic acid hydrochloride, 3-pyridylacetic acid hydrochloride, 4-pyridylacetic acid hydrochloride, (2-pyrimidylthio)acetic acid, pyruvic acid, tetrahydro-2-furoic acid, tetrahydro-3-furoic acid, thioctic acid, 2-thiopheneacetic acid, 3-thiopheneacetic acid, 2-thiophenecarboxylic acid, 3-thiophenecarboxylic acid, 2-thiopheneglyoxylic acid, (α,α,α-

trifluoro-p-tolyl)acetic acid, vinylacetic acid, acetoxyacetic acid, 2-benzofurancarboxylic acid, cinnoline-4-carboxylic acid, 3,5-diido-4-pyridone-1-acetic acid, 3,3-dimethylacrylic acid, ferrocenecarboxylic acid, 5-methoxy-1-indanone-3-acetic acid, 1-methyl-2-pyrrolecarboxylic acid, 3-oxo-1-indancarboxylic acid, trans-3-(3-pyridyl)acrylic acid, 3-(2-thienyl)acrylic acid, α,α,α-trifluoro-m-toluic acid, α,α,α-trifluoro-o-toluic acid, and α,α,α-trifluoro-p-toluic acid.

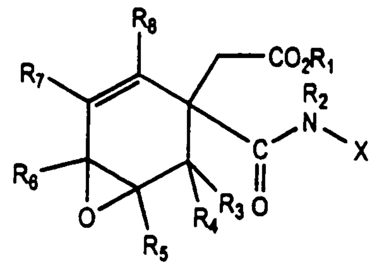
20. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

(a) synthesizing one or more epoxyol templates having the following structure:



wherein R_1-R_7 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

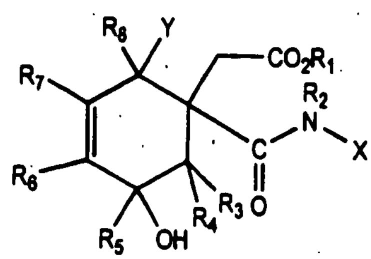
(b) reacting one or more ortho acetates with said one or more epoxyol templates to yield one or more diversifiable scaffolds having the following structure:



wherein R_1-R_8 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

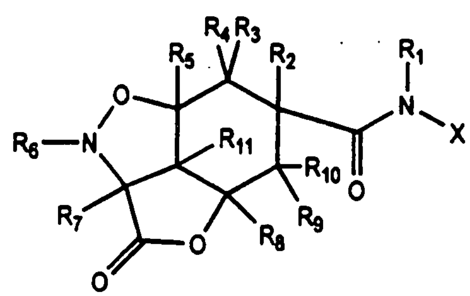
(c) diversifying said one or more scaffold structures at said one or more reactive moieties with one or more reagents or a skip codon to generate one or more isolated complex compounds reminiscent of natural products.

21. The method of claim 20, further comprising reaction with one or more palladium allylation catalysts and one or more nucleophiles after reaction with said one or more ortho acetates to yield one or more diversifiable scaffolds having the following structure:



wherein R_1-R_8 is selected from the group consisting of hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amin , hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X is selected from the group consisting of, any of the above, a solid support, a biomolecule and polymer; and Y is a nucleophiles selected from the group consisting of amine, phenol, maleonate, thiol, carboxylic acid, and azide.

22. The method of claim 21, further comprising reaction with one or more nitrones after reaction with said one or more palladium catalysts to generate one or more diversifiable scaffolds having the following structure:



wherein R_1-R_{11} is selected from the group consisting of, hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle, wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X is any of the above, a solid support unit, a biomolecule or polymer.

23. The method of claim 20, 21, or 22, wherein synthesizing said epoxyol template comprises:

providing (-)-shikimic acid;

reacting shikimic acid with DEAD and triphenylphosphine to yield an epoxide;

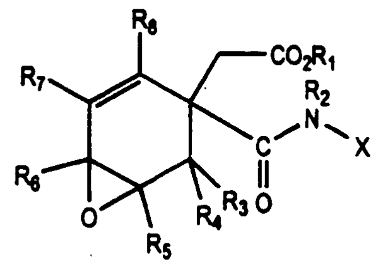
reacting said epoxide with benzoic acid, triphenylphosphine and DEAD to yield the benzoate ester;

reaction of said benzoate ester with lithium hydroxide to yield a carboxylic acid epoxyol template.

24. The method of claim 20, 21, or 22, further comprising attachment of said one or more epoxyol templates to a solid support prior to the step of synthesizing said one or more diversifiable scaffold structures.

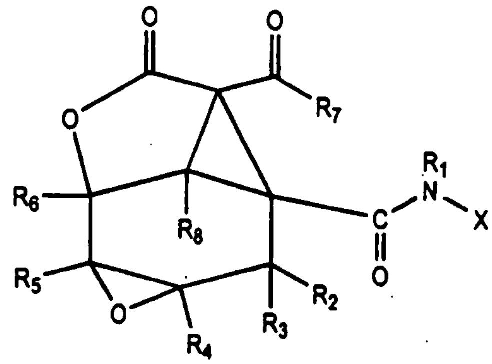
25. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

(a) synthesizing one or more epoxyol templates having the following structure:



wherein R_1-R_8 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting said one or more epoxyol templates with one or more acylating agents, tosyl azide, and a catalyst capable of effecting cyclopropanation to yield one or more scaffolds having the following structure:



wherein R_1-R_8 independently comprises any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted or unsubstituted heterocyclyl wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and wherein X is any of the above, a solid support, or any biomolecule or polymer.

(c) diversifying said one or more solid support bound scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

26. The method of claim 25, wherein synthesizing said epoxyol template comprises:

providing (-)-shikimic acid;

reacting shikimic acid with DEAD and triphenylphosphine to yield an epoxide;

reaction of said epoxide with benzoic acid, triphenylphosphine and DEAD to yield the benzoate ester;

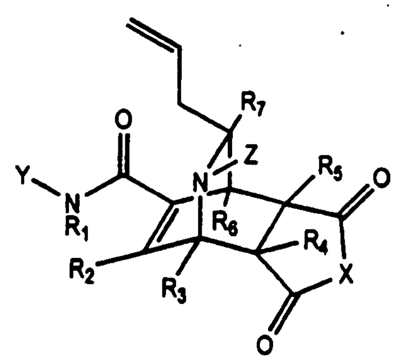
reaction of said benzoate ester with lithium hydroxide to yield a carboxylic acid epoxyol template.

27. The method of claim 25, further comprising attachment of each of said one or more epoxyol templates to one or more solid support units prior to the step of synthesizing said one or more diversifiable scaffold structures.

28. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

(a) providing one or more isonicotinamide templates;

(b) reacting said one or more isonicotinamide templates with one or more nucleophilic acylation reagents, dienophiles and amines to yield one or more diversifiable isoquinuclidine scaffolds having the following structure:

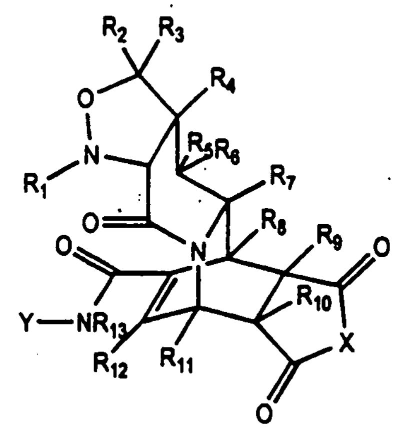


wherein R_1-R_7 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is NR, wherein R

includes, but is not limited to any substituted or unsubstituted alkyl or aryl moiety, CH_2, O or S; Y is hydrogen, solid support unit, a polymer or a biomolecule, and Z is hydrogen or indole.

(c) diversifying said one or more scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

29. The method of claim 28, further comprising reacting said one or more isoquinuclidine scaffolds with one or more nitrones to generate one or more diversifiable polycyclic alkaloid scaffold structures having the following structure:



wherein R_{10}-R_{13} is hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle, wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X includes, but is not limited to NR, wherein R includes, but is not limited to, any substituted or unsubstituted alkyl or aryl moiety, CH_2, O, or S; and Y includes, but is not limited to, hydrogen, a solid support unit, a polymer or biomolecule.

30. The method of claim 28 or 29, further comprising attachment of each of said one or more template structures to a solid support unit prior to the step of synthesizing said one or more diversifiable scaffold structures.

31. The method of claim 28 or 29, wherein synthesizing said one or more isonicotinamide template structures comprises synthesizing said one or more template structures directly on a solid support unit.

32. The method of claim 31, wherein synthesis of said isonicotinamide template structure directly on a solid support unit comprises:

providing nitrobenzylsulfonyl chloride;

reacting said sulfonyl chloride with a solid support unit to generate a solid support bound sulfonamide;

reacting said solid support bound sulfonamide with a substituted alcohol, triphenylphosphine or tributylphosphine and DEAD or TMAD (N, N', N", N'"-tetramethylazodicarboxamide) to generate a solid support bound sulfonamide containing a diversity position;

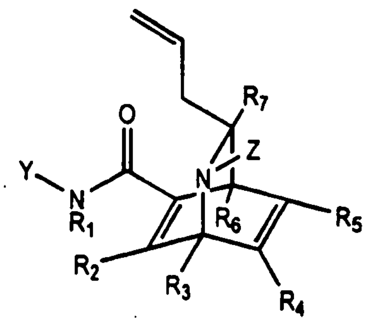
reacting said solid support bound sulfonamide with thiophenylate, wherein the counterion is selected from the group consisting of sodium, potassium, cesium, and amine bases, and wherein said amine base is selected from the group consisting of DBU, MTBD, DIPEA and triethylamine;

reacting said diversifiable support bound moiety with isonicotinoyl chloride to yield an isonicotinamide derivative containing a diversity position.

33. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

(a) providing one or more isonicotinamide templates;

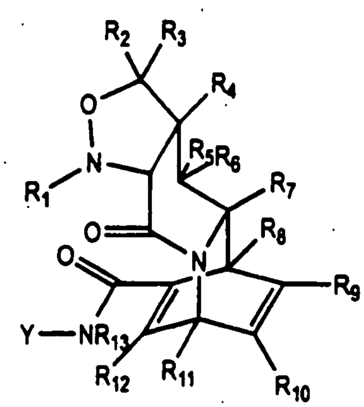
(b) reacting said one or more isonicotinamide templates with one or more nucleophilic acylation reagents, dienophiles and amines to yield one or more diversifiable isoquinuclidine scaffolds having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; wherein Y is a hydrogen, solid support unit, a polymer or a biomolecule; and Z is a hydrogen or indole; and

(c) diversifying said one or more scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

34. The method of claim 33, further comprising reacting said one or more isoquinuclidine scaffolds with one or more nitrones to generate one or more diversifiable polycyclic alkaloid scaffold structures having the following structure:



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35. The method of claim 33 or 34, further comprising attachment of each of said one or more template structures to a solid support unit prior to the step of synthesizing said one or more diversifiable scaffold structures.

36. The method of claim 33 or 34, wherein synthesizing an isonicotinamide template structure comprises synthesizing said template structure directly on a solid support unit.

37. The method of claim 36, wherein synthesis of said isonicotinamide template structure directly on a solid support unit comprises:

providing nitrobenzylsulfonyl chloride;

reacting said sulfonyl chloride with a solid support unit to generate a solid support bound sulfonamide;

reacting said solid support bound sulfonamide with a substituted alcohol, triphenylphosphine or tributylphosphine and DEAD or TMAD to generate a solid support bound sulfonamide containing a diversity position;

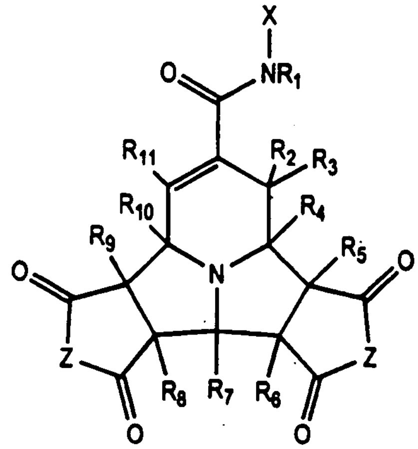
reacting said solid support bound sulfonamide with thiophenylate;

reacting said diversifiable support bound moiety with isonicotinoyl chloride to yield an isonicotinamide derivative containing a diversity position.

38. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

providing one or more isonicotinamide templates;

reacting said one or more isonicotinamide templates with bromoacetophenone, triethylamine, and a double bond containing electron withdrawing group to yield one or more diversifiable piperidine scaffolds having the following structure:



wherein R_1-R_{11} each independently comprise hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle, wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X is any of the above, a solid support, a biomolecule or a polymer; and Z is NR, wherein R is any substituted or unsubstituted alkyl or aryl moiety, CH_2, O or S.

diversifying said one or more piperdine scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

39. The method of claim 38, further comprising attachment of each of said one or more template structures to a solid support unit prior to the step of synthesizing said one or more diversifiable scaffold structures.

40. The method of claim 38, wherein synthesizing one or more isonicotinamide template structures comprises synthesizing said one or more template structures directly on a solid support unit.

41. The method of claim 38, wherein said method of synthesizing an isonicotinamide template directly on a solid support unit comprises:

providing nitrobenzenesulfonylchloride;

reacting said sulfonylchloride with a solid support unit to generate a solid support bound sulfonamide;

reacting said solid support bound sulfonamide with a substituted alcohol, triphenylphosphine or tributylphosphine, and DEAD or TMAD to generate a solid support bound sulfonamide containing a diversity position;

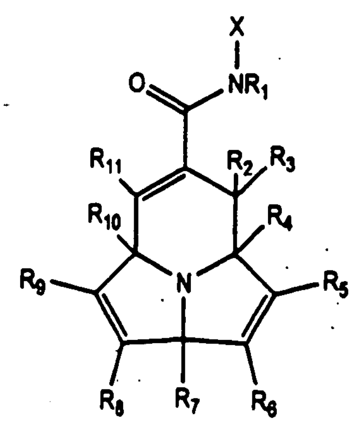
reacting said solid support bound sulfonamide with thiophenylate;

reacting said diversifiable support bound moiety with isonicotinoyl chloride to yield an isonicotinamide derivative containing a diversity position.

42. A method for generating one or more isolated complex compounds reminiscent of natural products comprising:

providing one or more isonicotinamide templates;

reacting said one or more isonicotinamide templates with bromoacetophenone, triethylamine, and a double bond containing electron withdrawing group to yield one or more diversifiable piperidine scaffolds having the following structure:



wherein R_1-R_{11} each independently include hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl,

acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X is any of the above, a solid support, a biomolecule or polymer; and

diversifying said one or more piperdine scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

43. The method of claim 42, further comprising attachment of each of said one or more template structures to a solid support unit prior to the step of synthesizing said one or more diversifiable scaffold structures.

44. The method of claim 42, wherein providing said one or more isonicotinamide templates comprises synthesizing said template structure directly on a solid support unit.

45. The method of claim 44, wherein said method of providing a solid support bound isonicotinamide template comprises:

providing nitrobenzenesulfonylchloride;

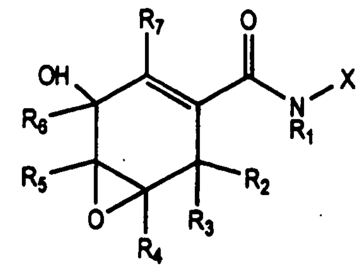
reacting said sulfonylchloride with a solid support unit to generate a solid support bound sulfonamide;

reacting said solid support bound sulfonamide with a substituted alcohol, triphenylphosphine or tributylphosphine, and DEAD or TMAD to generate a solid support bound sulfonamide containing a diversity position;

reacting said solid support bound sulfonamide with thiophenoxide, wherein the counterion is selected from the group consisting of sodium, potassium, cesium, and amine bases, and wherein said amine bases are selected from the group consisting of DBU, MTBD, DIPEA, and triethylamine; and

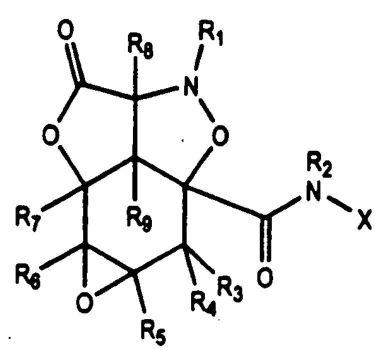
reacting said diversifiable support bound moiety with isonicotinoyl chloride to yield an isonicotinamide derivative containing a diversity position.

46. A library of templates for use in the development of complex compounds reminiscent of natural products comprising the structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

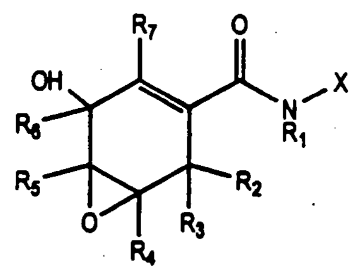
47. A library of isolated complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_9 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

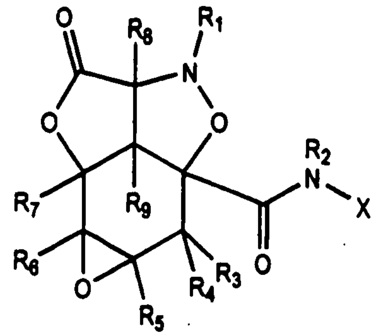
48. The library of claim 47 produced by the method comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

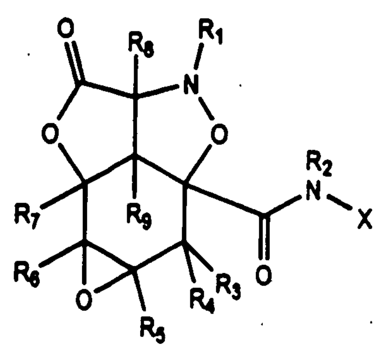
(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:



wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

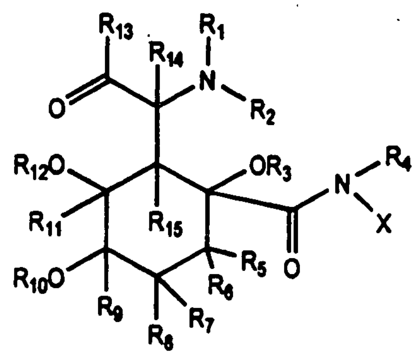
49. An isolated natural product-like compound comprising the following structure:



wherein R_1-R_9 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

50. The composition of claim 49, wherein X comprises a solid support unit.

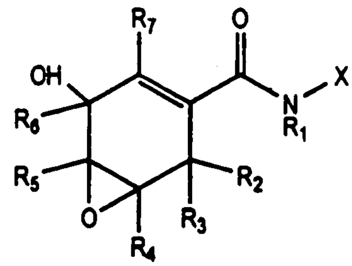
51. A library of isolated complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_{14} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

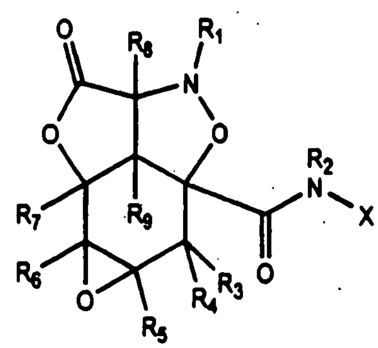
52. The library of claim 51 produced by the process comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:

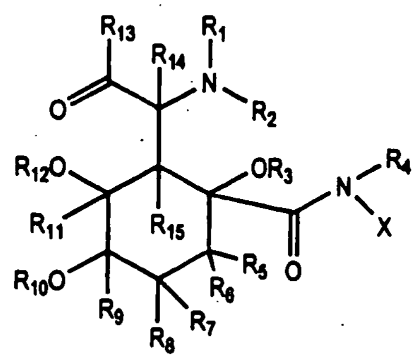


wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl,

thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

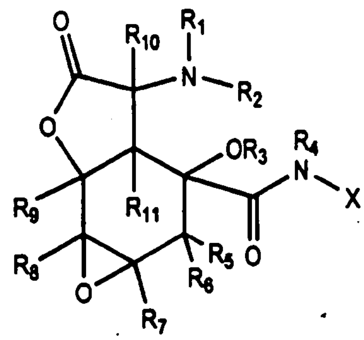
53. A natural product-like compound comprising the following structure:



wherein R_1-R_{14} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

54. The compound of claim 53, wherein X is a solid support unit.

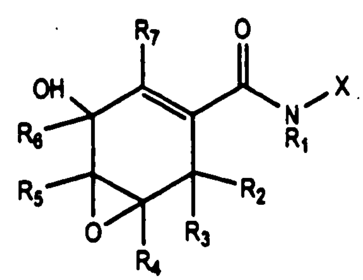
55. A library of isolated complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_{11} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

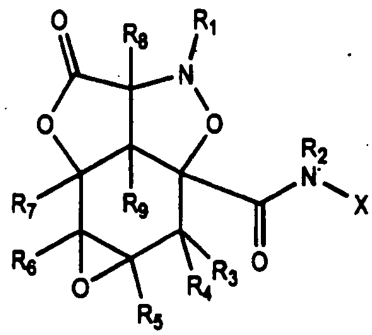
56. The library of claim 55 produced by the process comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalk xy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

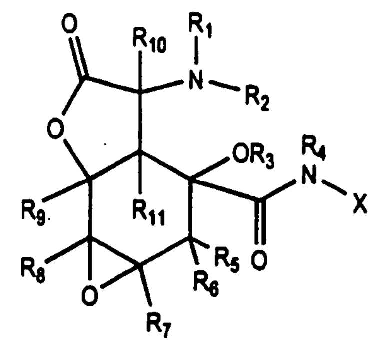
(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:



wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

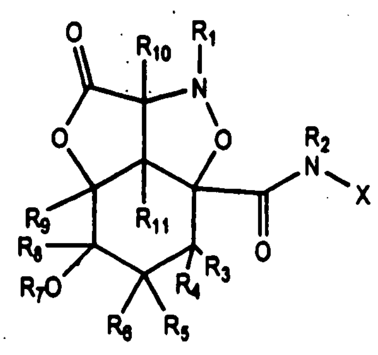
57. A natural product-like compound comprising the following structure:



wherein R_1-R_{11} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

58. The compound of claim 57, wherein X comprises a solid support unit.

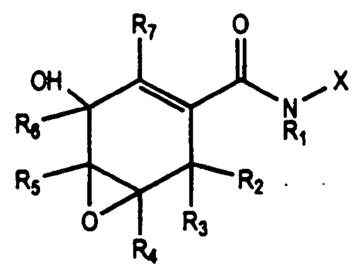
59. A library of isolated complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_{11} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

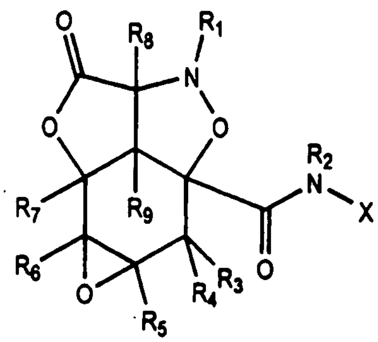
60. The library of claim 59 produced by the process comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

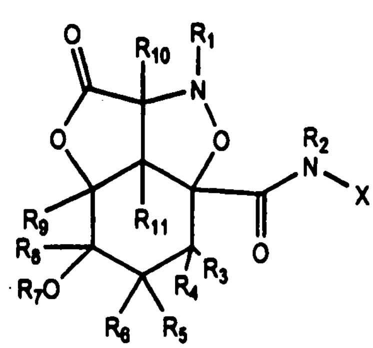
(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:



wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

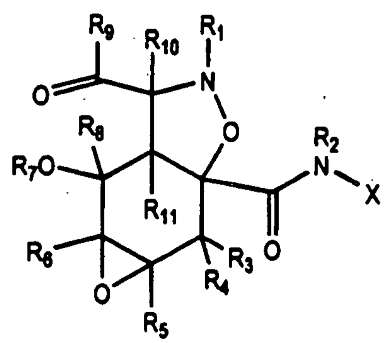
61. A natural product-like compound comprising the following structure:



wherein R_1-R_{11} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

62. The compound of claim 61, wherein X comprises a solid support unit.

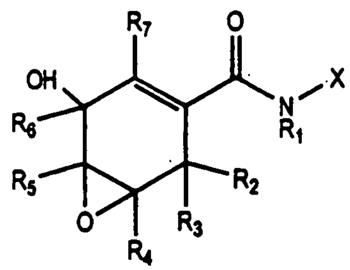
63. A library isolated complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_{11} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

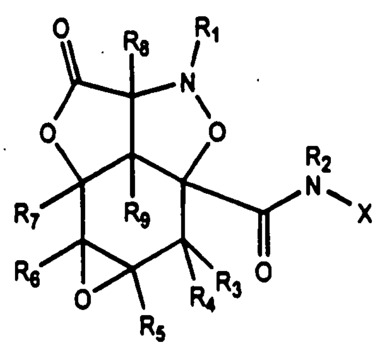
64. The library of claim 63 produced by the process comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:

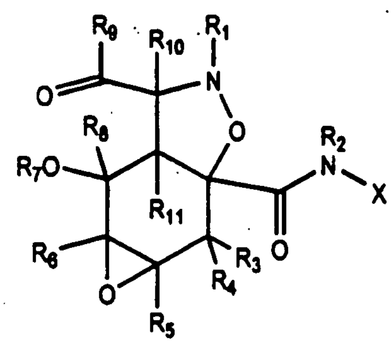


wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl,

thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

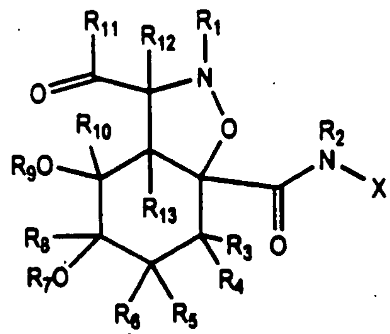
65. A natural product-like compound comprising the following structure:



wherein R_1-R_{11} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

66. The compound of claim 65, wherein X comprises a solid support unit.

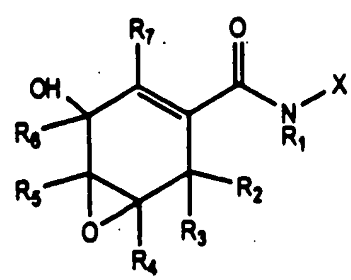
67. A library of isolated complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

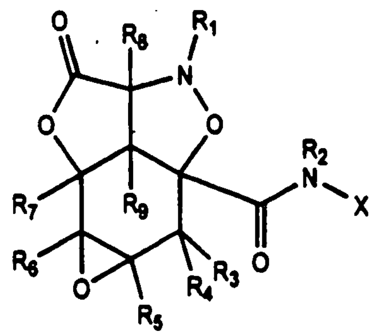
68. The library of claim 67 produced by the process comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

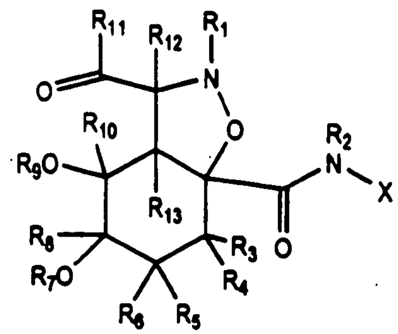
(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:



wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

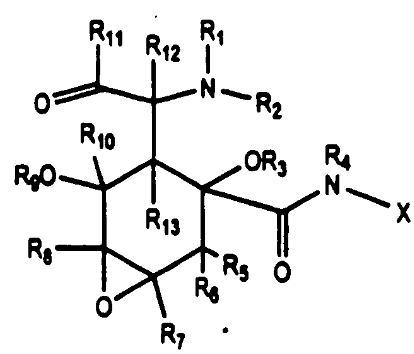
69. A natural product-like compound comprising the following structure:



wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

70. The compound of claim 69, wherein X comprises a solid support unit.

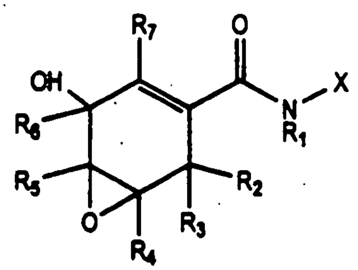
71. A library of isolated complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

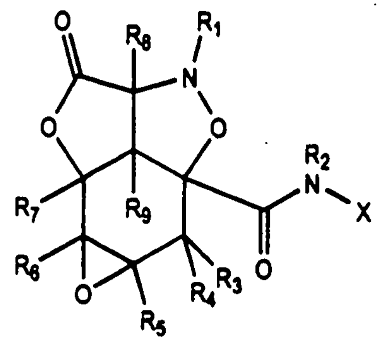
72. The library of claim 71 produced by the process comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocyce is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

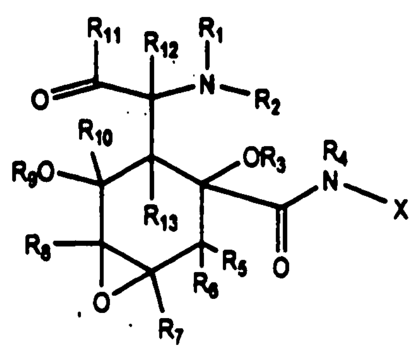
(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:



wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

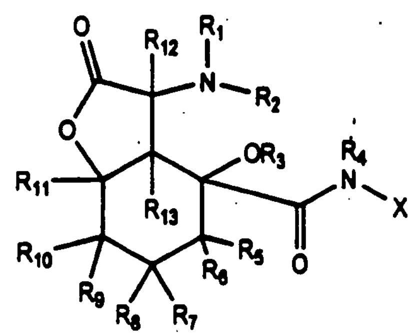
73. A natural product-like compound comprising the following structure:



wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

74. The compound of claim 73, wherein X comprises a solid support unit.

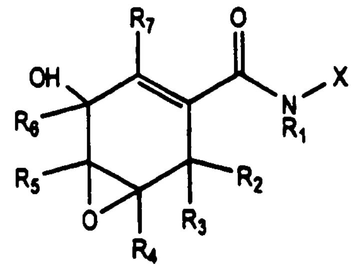
75. A library of natural product-like compounds having the following structure:



wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

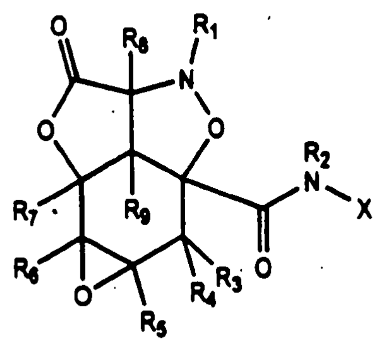
76. The library of claim 75 produced by the process comprising:

(a) synthesizing one or more expoxyol templates having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocyce is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting one or more nitrone carboxylic acids with said one or more expoxyol templates to yield one or more diversifiable tetracyclic scaffolds having the following structure:

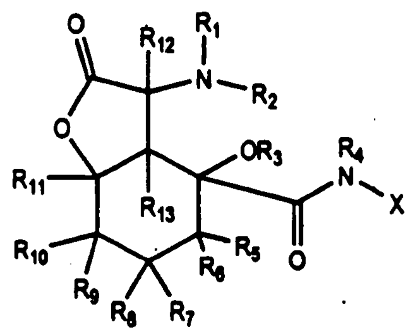


wherein R_1-R_9 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents

selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(c) diversifying said one or more tetracyclic scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more complex compounds reminiscent of natural products.

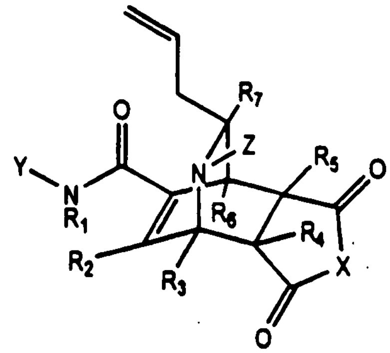
77. A natural product-like compound comprising the following structure:



wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

78. The compound of claim 77, wherein X comprises a solid support unit.

79. A library isolated complex compounds reminiscent of natural products having the following structure:

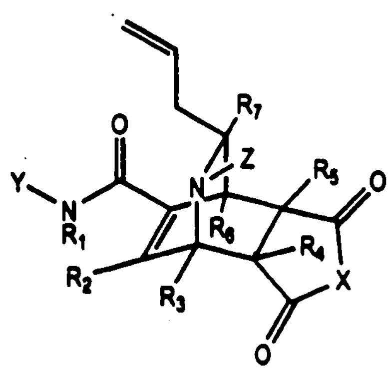


wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycly is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; wherein X is NR, wherein R inlcudes but is not limited to any substituted or unsubstitued alkyl or aryl moiety, CH_2, O, or S; Y is hydrogen, a solid support unit, a polymer or biomolecule; and Z is hydrogen or indole.

80. The library of claim 79 produced by the process comprising:

(a) providing one or more isonicotinamide templates;

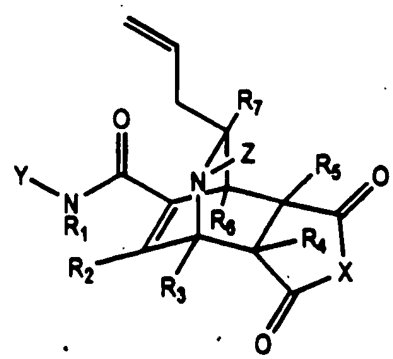
(b) reacting said one or more isonicotinamide templates with one or more nucleophilic acylation reagents, dienophiles and amines to yield one or more diversifiable isoquinuclidine scaffolds having the following structure:



wherein R_1-R_7 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is NR, wherein R includes, but is not limited to any substituted or unsubstituted alkyl or aryl moiety, CH_2, O or S; Y is hydrogen, solid support unit, a polymer or a biomolecule, and Z is hydrogen or indole.

(c) diversifying said one or more scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

81. A natural product-like compound comprising the following structure:

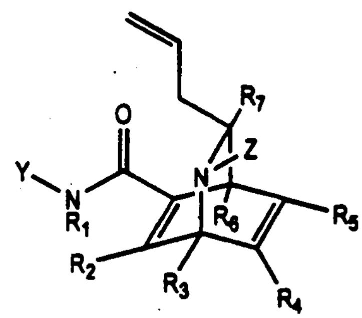


wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycly is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; wherein X is NR, wherein R

inlcudes but is not limited to any substituted or unsubstitued alkyl or aryl moiety, CH_2, O, or S; Y is hydrogen, a solid support unit, a polymer or biomolecule; and Z is hydrogen or indole.

82. The compound of claim 81, wherein X comprises a solid support unit.

83. A library of isolated complex compounds reminiscent of natural products having the following structure:

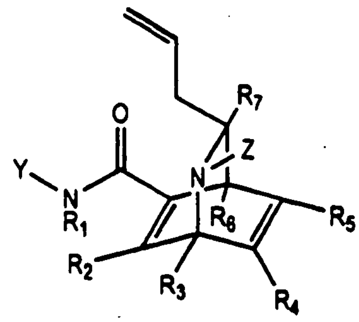


wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycly is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; wherein Y is hydrogen, a solid support unit, a polymer or biomolecule; and Z is hydrogen or indole.

84. The library of claim 83 produced by the process comprising:

(a) providing one or more isonicotinamide templates;

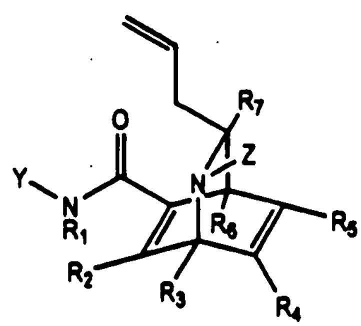
(b) reacting said one or more isonicotinamide templates with one or more nucleophilic acylation reagents, dienophiles and amines to yield one or more diversifiable isoquinuclidine scaffolds having the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; wherein Y is a hydrogen, solid support unit, a polymer or a biomolecule; and Z is a hydrogen or indole; and

(c) diversifying said one or more scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

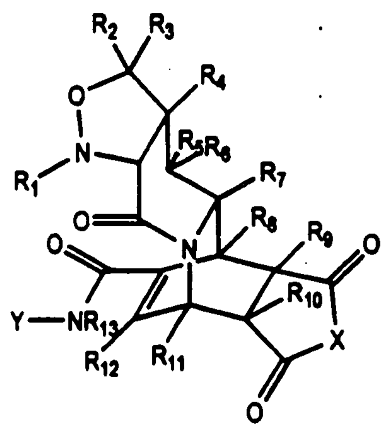
85. A natural product-like compound comprising the following structure:



wherein R_1-R_7 each independently comprises any linear or branched, substituted r unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycly is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; wherein Y is hydrogen, a solid support unit, a polymer or biomolecule; and Z is hydrogen or indole.

86. The compound of claim 85, wherein X comprises a solid support unit.

87. An isolated library of complex compounds reminiscent of natural products having the following structure:



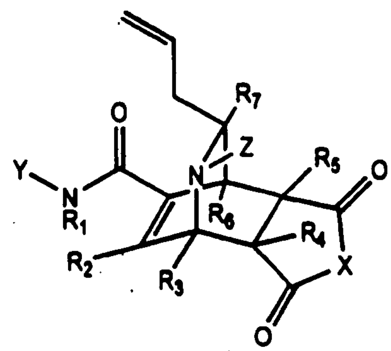
wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, hal , hydroxy, amino, thio, lower alk xy, lower alkylthi , lower alkylamino, nitro, phenoxy, benzyloxy; wherein X is

NR, wherein R is any substituted or unsubstituted alkyl or aryl moiety, CH_2, S or O; and Y is a solid support unit or hydrogen.

88. The library of claim 87 produced by the process comprising:

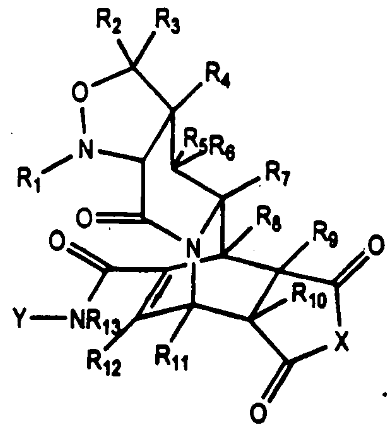
(a) providing one or more isonicotinamide templates;

(b) reacting said one or more isonicotinamide templates with one or more nucleophilic acylation reagents, dienophiles and amines to yield one or more diversifiable isoquinuclidine scaffolds having the following structure:



wherein R_1-R_7 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is NR, wherein R includes, but is not limited to any substituted or unsubstituted alkyl or aryl moiety, CH_2, O or S; Y is hydrogen, solid support unit, a polymer or a biomolecule, and Z is hydrogen or indole;

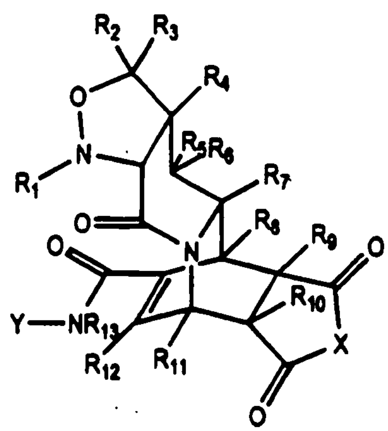
(c) reacting said one or more isoquinuclidine scaffolds with one or more nitrones to generate one or more diversifiable polycyclic alkaloid scaffold structures having the following structure:



; and

(d) diversifying said one or more scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

89. A natural product-like compound comprising the following structure:

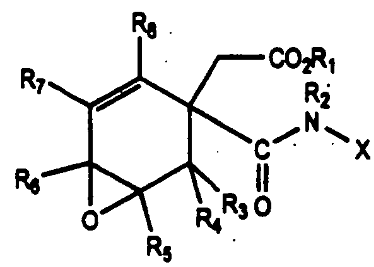


wherein R_1-R_{13} each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen,

cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, hal , hydroxy, amino, thio, lower alk xy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; wherein X is NR, wherein R is any substituted or unsubstituted alkyl or aryl moiety, CH_2, S or O; and Y is a solid support unit or hydrogen.

90. The compound of claim 90, wherein X comprises a solid support unit.

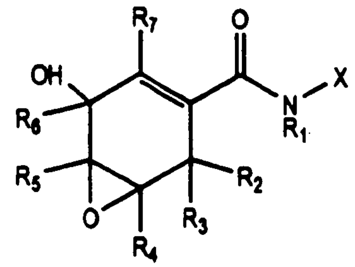
91. A library of isolated complex compounds reminiscent of natural products having the following structure:



wherein R_1-R_8 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

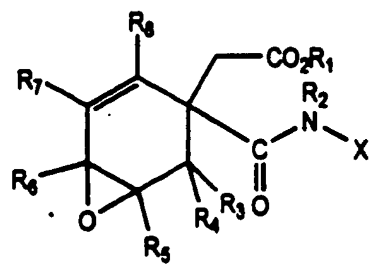
92. The library of claim 91 produced by the process comprising:

(a) synthesizing one or more epoxyol templates having the following structure:



wherein R_1-R_7 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting one or more ortho acetates with said one or more epoxyol templates to yield one or more diversifiable scaffolds having the following structure:

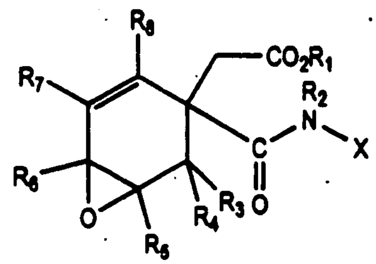


wherein R_1-R_8 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, hal , hydroxy, amino, thio, lower alkoxy,

lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

(c) diversifying said one or more scaffold structures at said one or more reactive moieties with one or more reagents or a skip codon to generate one or more isolated complex compounds reminiscent of natural products.

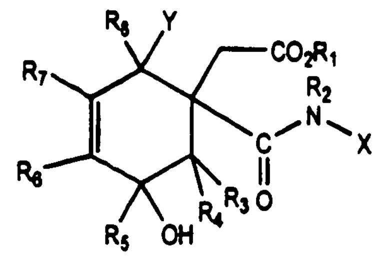
93. An isolated natural product-like compound comprising the following structure:



wherein R_1-R_8 each independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer.

94. The compound of claim 93, wherein X comprises a solid support unit.

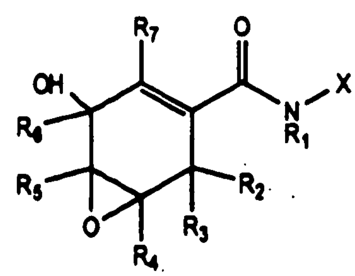
95. An isolated library of complex compounds reminiscent of natural products comprising the following structure:



wherein R_1-R_8 each independently comprises hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted heterocycle, wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X is any of the above, a solid support, a biomolecule or polymer; and Y is a nucleophile selected from the group consisting of amine, phenol, maleonate, thiol, carboxylic acid, and azide.

96. The library of claim 95 produced by the process comprising:

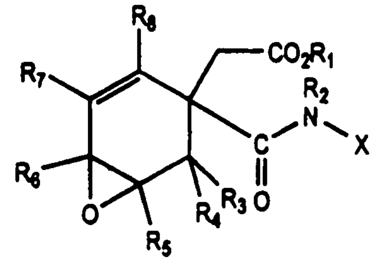
(a) synthesizing one or more epoxyol templates having the following structure:



wherein R_1-R_7 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents

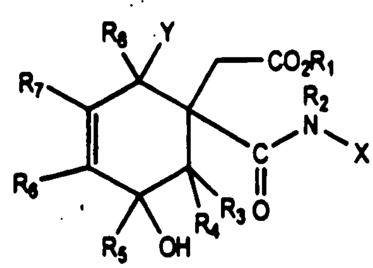
selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting one or more ortho acetates with said one or more epoxyol templates to yield one or more diversifiable scaffolds having the following structure:



wherein R_1-R_8 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer; and

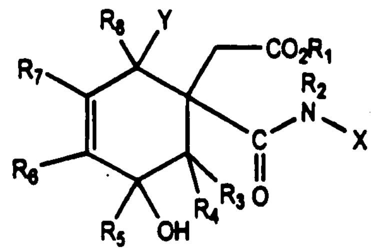
(c) reaction with one or more palladium allylation catalysts and one or more nucleophiles after reaction with said one or more ortho acetates to yield one or more diversifiable scaffolds having the following structure:



; and

(d) diversifying said one or more scaffold structures at said one or more reactive moieties with one or more reagents or a skip codon to generate one or more isolated complex compounds reminiscent of natural products.

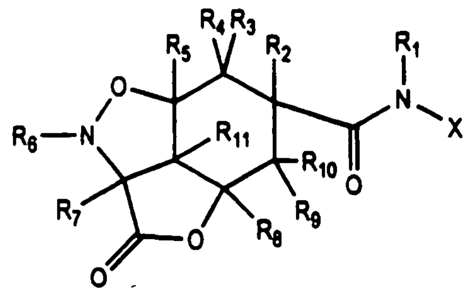
97. An isolated natural product-like compound comprising the following structure:



wherein R_1-R_8 each independently comprises hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted heterocycle, wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X is any of the above, a solid support, a biomolecule or polymer; and Y is a nucleophile selected from the group consisting of amine, phenol, maleonate, thiol, carboxylic acid, and azide.

98. The compound of claim 97, wherein X comprises a solid support unit.

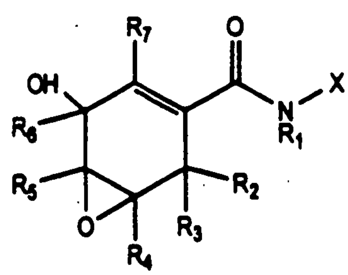
99. An library of isolated complex compounds reminiscent of natural products having the following structure:



wherein R_1-R_{11} each independently comprise hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstitued heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X is any of the above, a solid support unit, biomolecule or polymer.

100. The library of claim 99 produced by the process comprising:

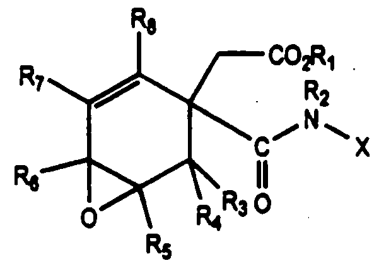
(a) synthesizing one or more epoxyol templates having the following structure:



wherein R_1-R_7 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbam yl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents

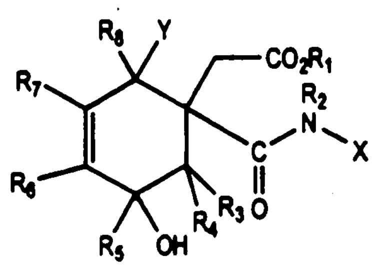
selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

(b) reacting one or more ortho acetates with said one or more epoxyol templates to yield one or more diversifiable scaffolds having the following structure:

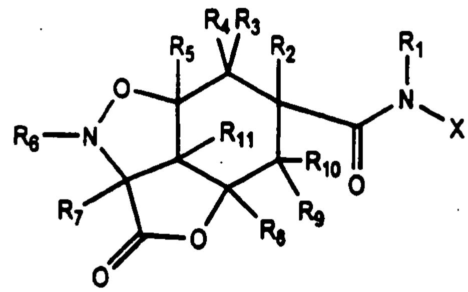


wherein R_1-R_8 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer; and

(c) reaction with one or more palladium allylation catalysts and one or more nucleophiles after reaction with said one or more ortho acetates to yield one or more diversifiable scaffolds having the following structure:



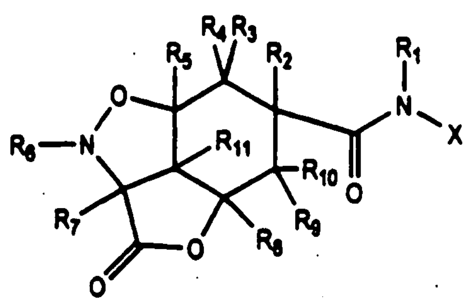
(d) reaction with one or more nitrones after reaction with said one or more palladium catalysts to generate one or more diversifiable scaffolds having the following structure:



wherein R_1-R_{11} is selected from the group consisting of, hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle, wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X is any of the above, a solid support unit, a biomolecule or polymer; and

(e) diversifying said one or more scaffold structures at said one or more reactive moieties with one or more reagents or a skip codon to generate one or more isolated complex compounds reminiscent of natural products.

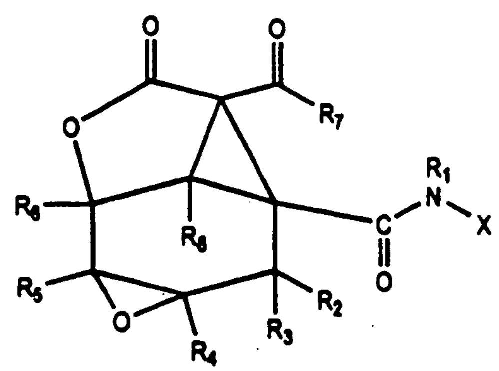
101. An isolated natural product-like compound comprising the following structure:



wherein R_1-R_{11} each independently comprise hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstitued heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X is any of the above, a solid support unit, biomolecule or polymer.

102. The compound of claim 101, wherein X comprises a solid support unit.

103. A library of isolated complex compounds reminiscent of natural products having the following structure:

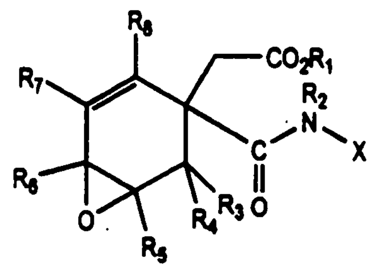


wherein R_1-R_8 independently comprises any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylallkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy,

lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and whrein X is any of the above, a solid support, or any biomolecule or polymer.

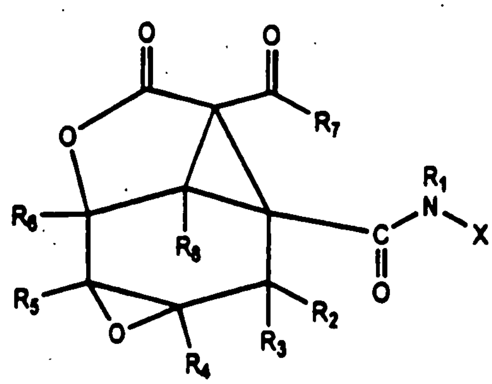
104. The library of claim 103 produced by the process comprising:

(a) synthesizing one or more epoxyol templates having the following structure:



wherein R_1-R_8 independently comprises any linear or branched, substituted or unsubstituted alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy; and wherein X is any of the above, hydrogen, a solid support unit, a biomolecule or a polymer;

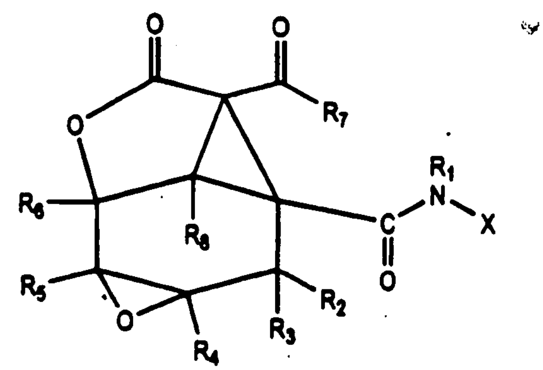
(b) reacting said one or more epoxyol templates with one or more acylating agents, tosyl azide, and a catalyst capable of effecting cyclopropanation to yield one or more scaffolds having the following structure:



wherein R_1-R_8 independently comprises any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted or unsubstituted heterocyclyl wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and whrein X is any of the above, a solid support, or any biomolecule or polymer; and

(c) diversifying said one or more solid support bound scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

105. An isolated natural product-like compound comprising the following structure:

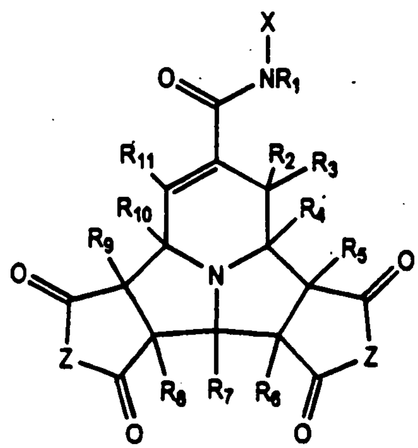


wherein R_1-R_8 independently comprises any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylallkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted

or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substitutents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and whrein X is any of the above, a solid support, or any biomolecule or polymer.

106. The compound of claim 105, wherein X comprises a solid support unit.

107. A library of isolated complex compounds reminiscent of natural products having the following structure:



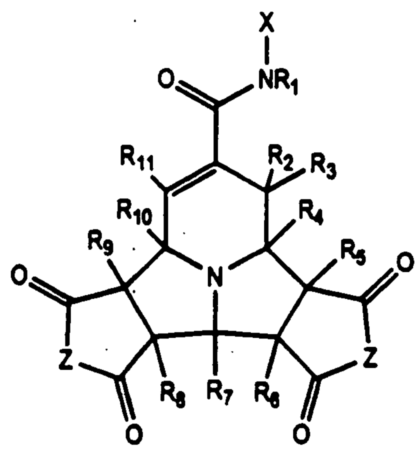
wherein R_1-R_{11} are any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylallkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and X is a any of the

above, a solid support, or any biomolecule or polymer; and Z is NR, wherein R is any substitued or unsubstituted alkyl or aryl moiety, CH_2, O, or S.

108. The library of claim 107 produced by the process comprising:

providing one or more isonicotinamide templates;

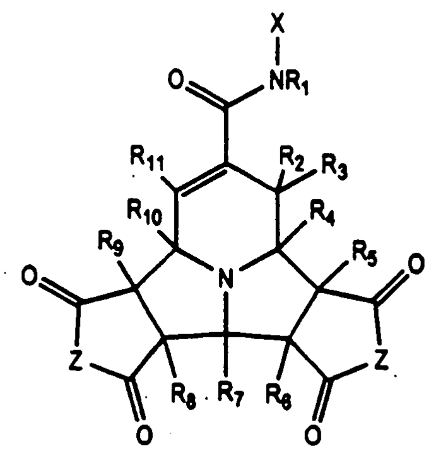
reacting said one or more isonicotinamide templates with bromoacetophenone, triethylamine, and a double bond containing electron withdrawing group to yield one or more diversifiable piperidine scaffolds having the following structure:



wherein R_1-R_{11} each independently comprise hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstituted heterocycle, wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; X is any of the above, a solid support, a biomolecule or a polymer; and Z is NR, wherein R is any substituted or unsubstituted alkyl or aryl moiety, CH_2, O or S.

diversifying said one or more piperdine scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

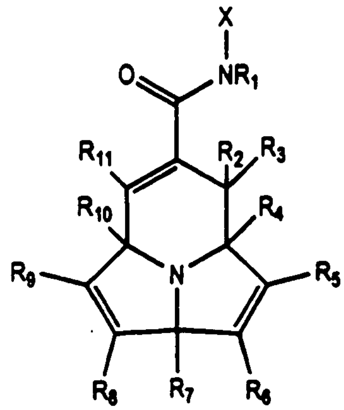
109. An isolated natural product-like compound comprising the following structure:



wherein R_1-R_{11} are any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylallkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and X is a any of the above, a solid support, or any biomolecule or polymer; and Z is NR, wherein R is any substitued or unsubstituted alkyl or aryl moiety, CH_2, O, or S.

110. The compound of claim 109, wherein X comprises a solid support unit.

111. A library of isolated complex compounds reminiscent of natural products having the following structure:

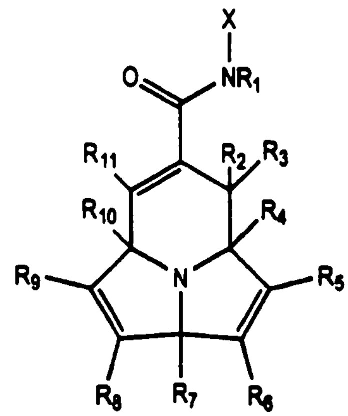


wherein R_1-R_{11} are independently any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylallkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and X is a any of the above, a solid support, or any biomolecule or polymer.

112. The library of claim 111 produced by the process comprising:

providing one or more isonicotinamide templates;

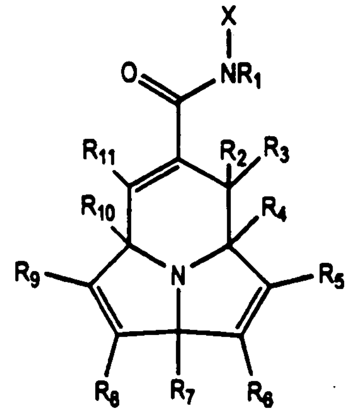
reacting said one or more isonicotinamide templates with bromoacetophenone, triethylamine, and a double bond containing electron withdrawing group to yield one or more diversifiable piperidine scaffolds having the following structure:



wherein R_1-R_{11} each independently include hydrogen, any linear or branched alkyl, alkenyl, aminoalkyl, acylamino, acyloxy, alkoxycarbonyl, alkoxy, alkylaryl, hydroxyalkyl, thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylalkoxy, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, any functionality incorporating phosphorous, and substituted or unsubstitued heterocycle wherein said substituted heterocycle is preferably substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, and benzyloxy; and X is any of the above, a solid support, a biomolecule or polymer; and

diversifying said one or more piperdine scaffold structures at one or more of said reactive moieties with one or more reagents or a skip codon, to generate one or more isolated complex compounds reminiscent of natural products.

113. An isolated natural product-like compound comprising the following structure:



wherein R_1-R_{11} are independently any linear or branched alkyl, alkenyl, linear or branched aminoalkyl, linear or branched acylamino, linear or branched acyloxy, linear or branched alkoxycarbonyl, linear or branched alkoxy, linear or branched alkylaryl, linear or branched hydroxyalkyl, linear or branched thioalkyl, acyl, amino, hydroxy, thio, aryloxy, arylallkoxy, hydrogen, alkynyl, halogen, cyano, sulfhydryl, carbamoyl, nitro, trifluoromethyl, and substituted or unsubstituted heterocycle wherein said heterocycle is substituted with 1-5 substituents selected from the group consisting of lower alkyl, halo, hydroxy, amino, thio, lower alkoxy, lower alkylthio, lower alkylamino, nitro, phenoxy, benzyloxy, and any derivative incorporating phosphorous; and X is a any of the above, a solid support, or any biomolecule or polymer.

114. The compound of claim 113, wherein X comprises a solid support unit.

115. A method for determining one or more biological activities of members of a library of compounds comprising:

subjecting a library to a biological target, wherein said library is an isolated complex library of compounds reminiscent of natural products;

determining a statistically significant change in a biochemical activity relative to the level of biochemical activity in the absence of the library of compounds; and

identification of the library members producing said statistically significant change.

116. A kit for determining one or more biological activities of a library member comprising:

providing a binding reagent; and

providing a library of compounds, wherein said library of compounds is an isolated complex library of compounds reminiscent of natural products.

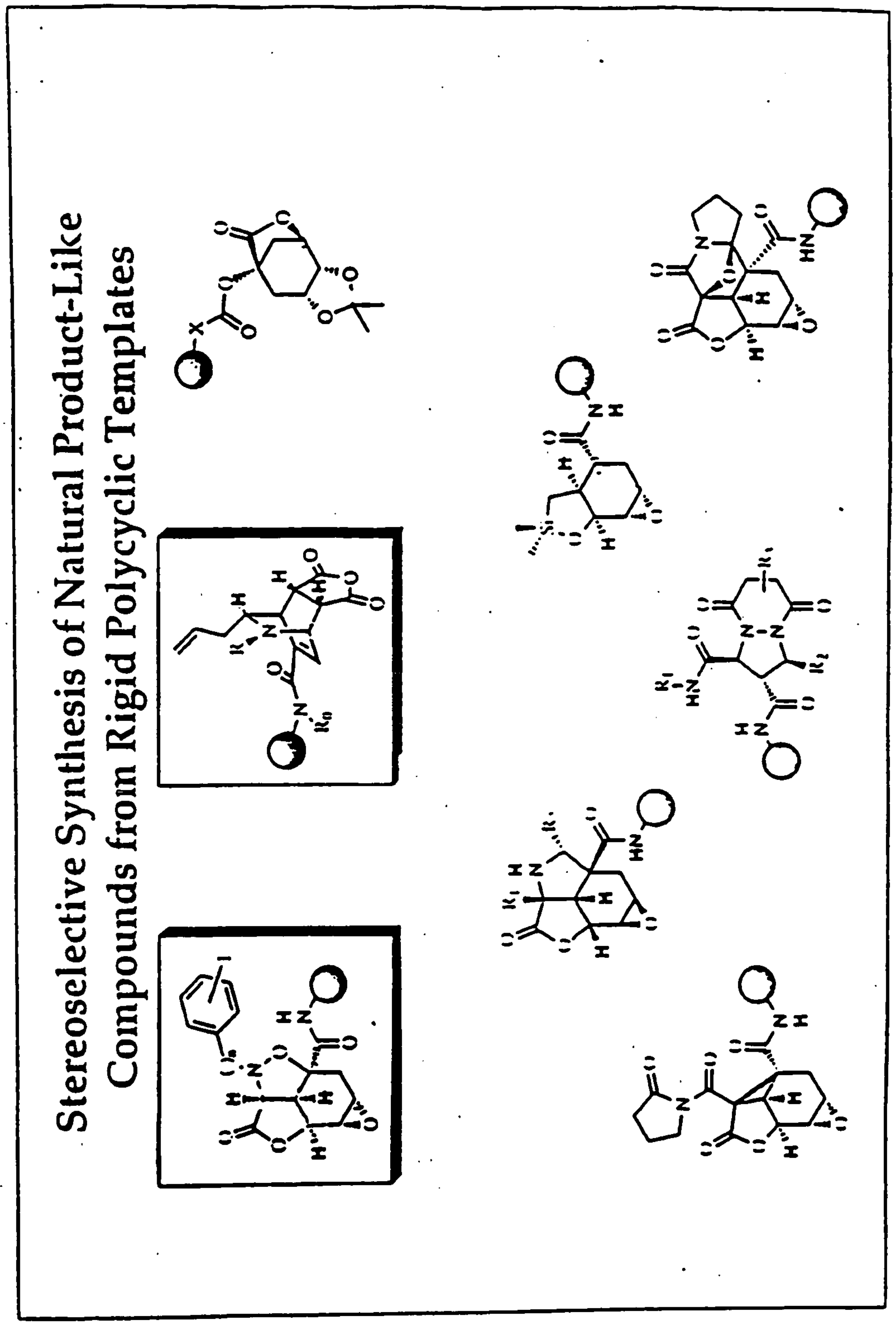

Stereoselective Synthesis of Natural Product-Like
Compounds from Rigid Polycyclic Templates

Figure 1

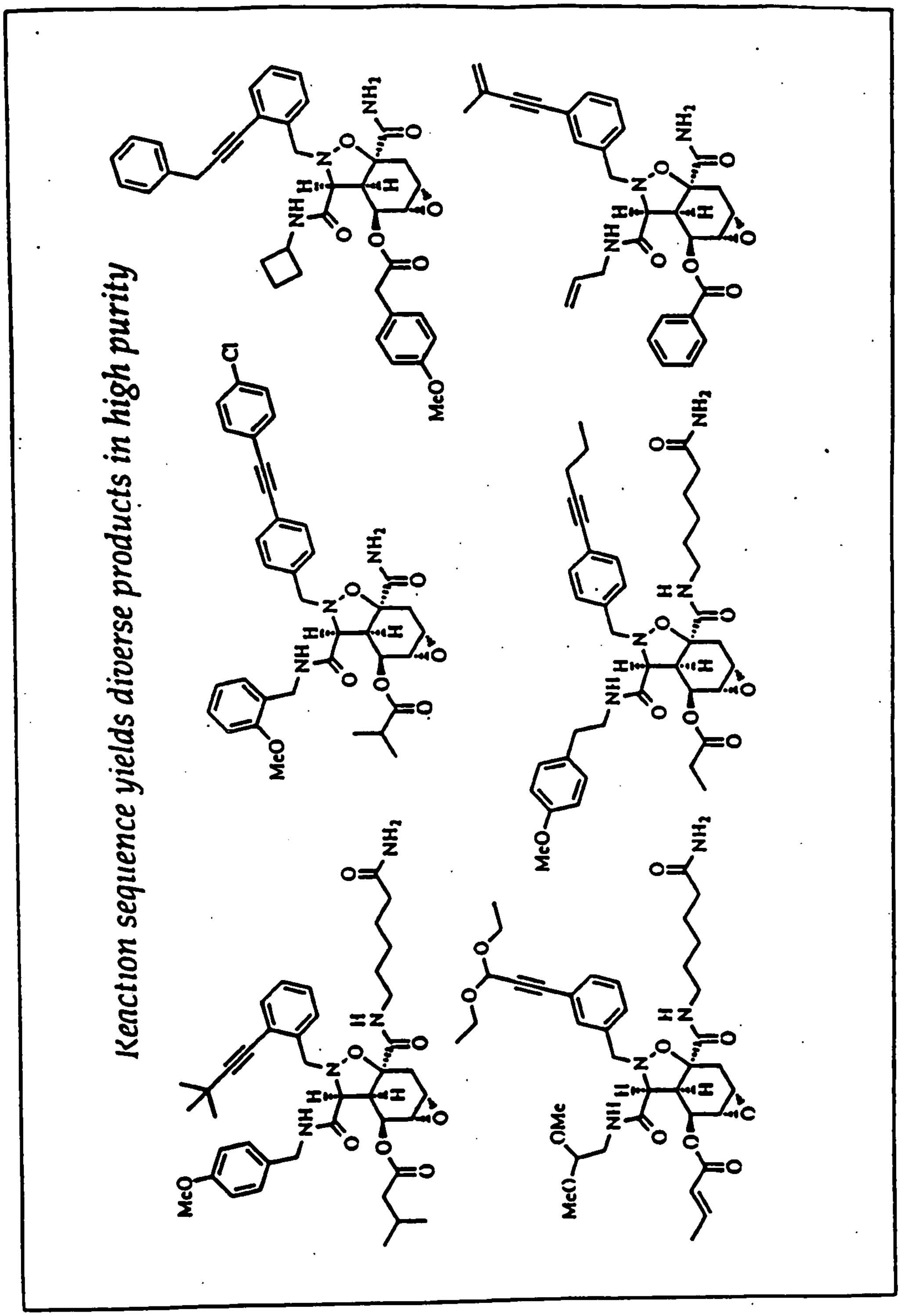
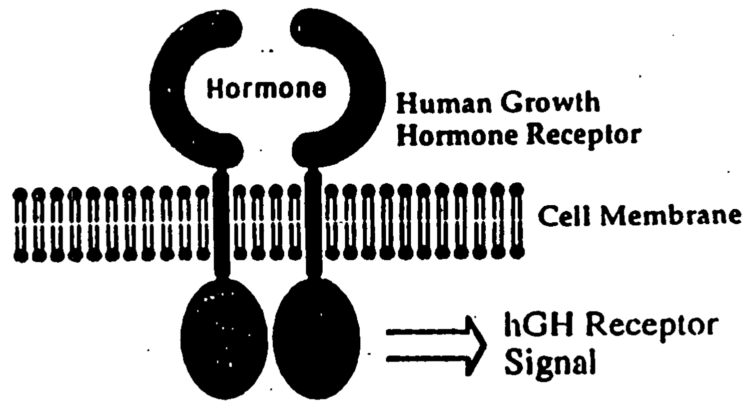


Figure 2

The Human Growth Hormone Receptor is a Target for Chemical Induced Direct Dimerization

Binding of human growth hormone to its symmetrical extracellular receptor induces homodimerization of the receptor and initiates the intracellular growth hormone signalling pathway. The "hot spot" a small patch of residues which were identified as being responsible for >85% of the binding energy between hGH and its receptor, is an excellent target for the library.



The radial small molecule library will be assayed for binding to the human growth hormone receptor. High affinity binders will be covalently homodimerized at the position where the solid phase was attached and tested for their ability to induce hGH receptor signalling. This would constitute the first example of direct dimerization by a small molecule dimer system. Applications to other signalling systems may also be possible based on our radial library.

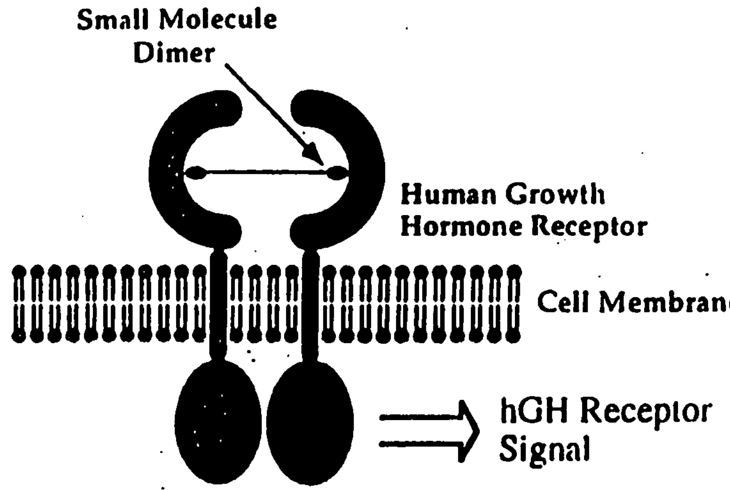
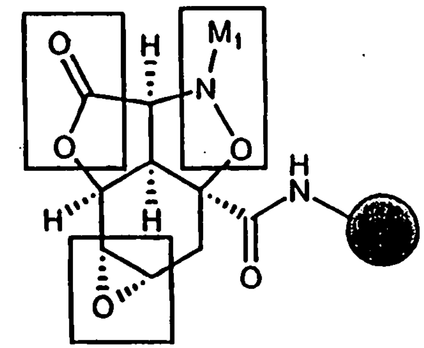
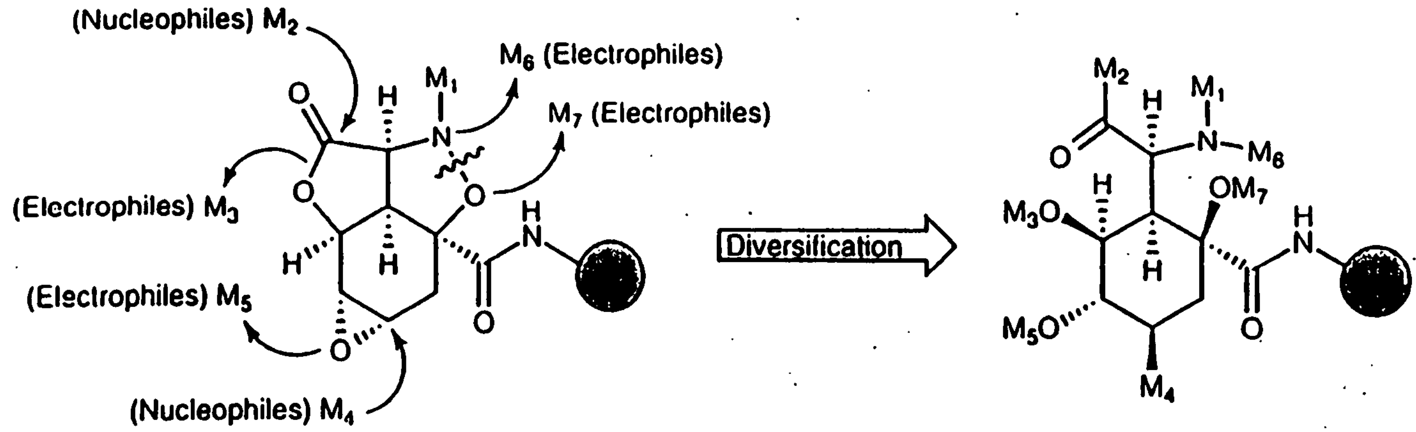


Figure 3

Diversity Expansion Can Be Acheived by Functional Group Manipulation

The boxed regions provide a high density of potential diversity nucleation points without the use of protecting groups.





Each chemical step will deliver a new monomer while *concurrently generating* a new position for functionalization.

Seven potential monomer sites radially arrayed.

Figure 4

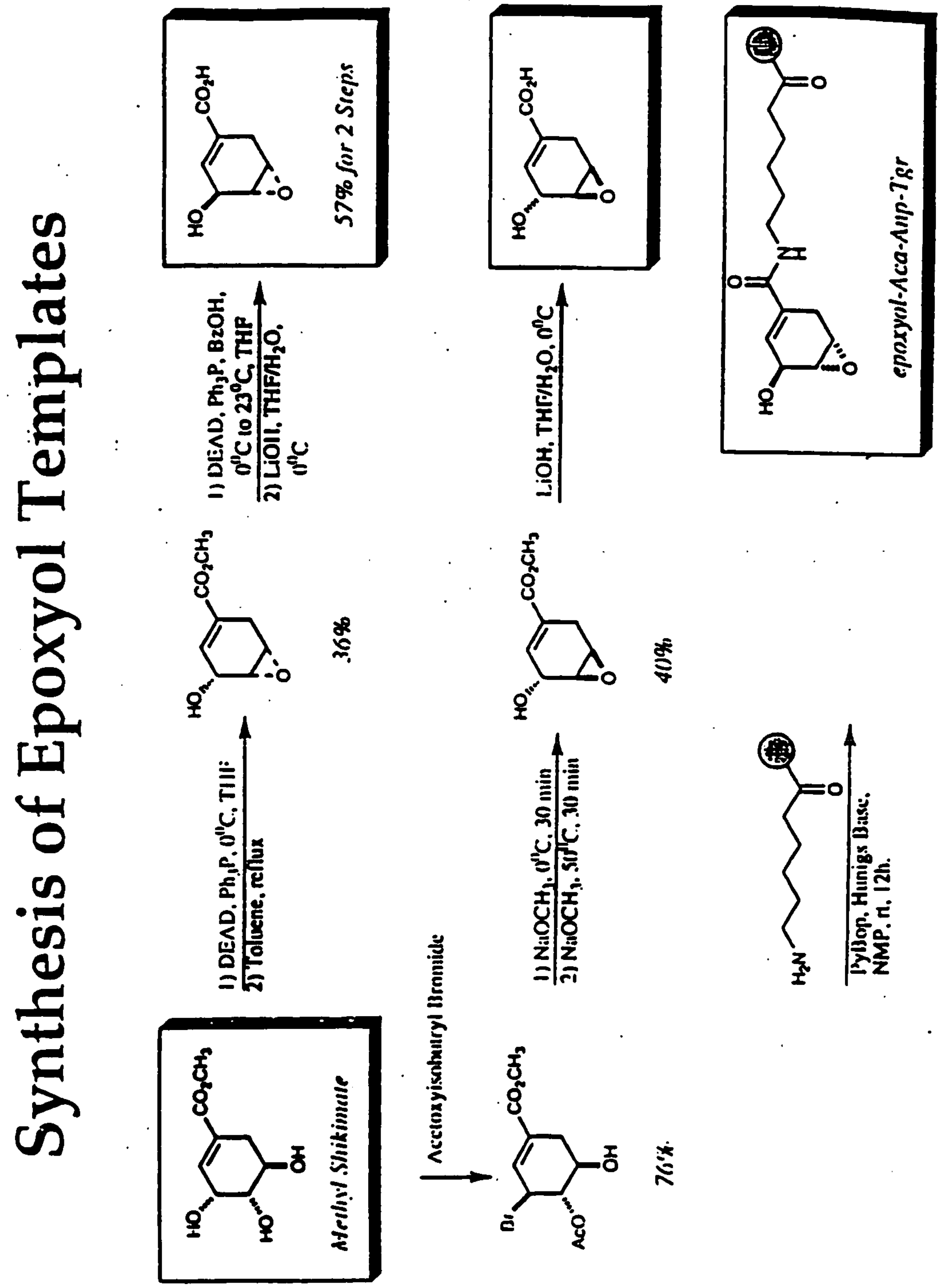

Synthesis of Epoxyol Templates
Methyl Shikimate
Acetoxyisobutyryl Bromide
76%
1) DEAD, Ph3P, 0°C, THF
2) Toluene, reflux
36%
1) NaOCH3, 0°C, 30 min
2) NaOCH3, 50°C, 30 min
40%
1) DEAD, Ph3P, BzOH, 0°C to 23°C, THF
2) LiOH, THF/H2O, 0°C
57% for 2 Steps
LiOH, THF/H2O, 0°C
PyBop, Hunigs Base, NMP, rt, 12h.
epoxyol-Aca-Amp-Tgr

Figure 5

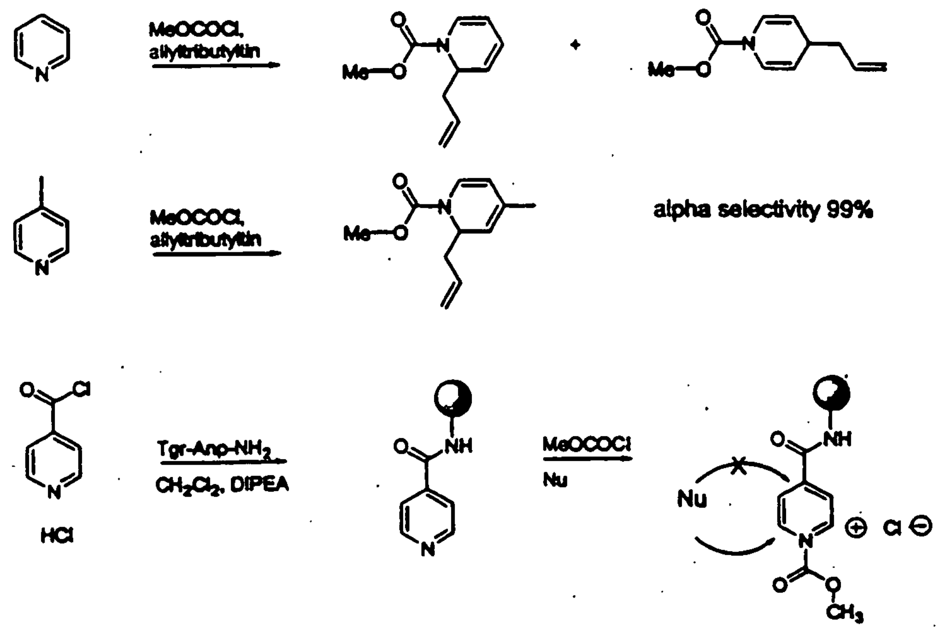

MeOCOCl,
allyltributyltin
Me—O
+
MeOCOCl,
allyltributyltin
alpha selectivity 99%
HCl
Tgr-Anp-NH$_2$
CH$_2$Cl$_2$, DIPEA
NH
MeOCOCl
Nu
Nu
Cl
CH$_3$

Figure 6

Solid Support for Combinatorial Chemistry

A Versatile Scaffold for On-Bead or Off-Bead Assay

Tentagel amino resin
- *Composite of low cross linked polystyrene and polyethylene glycol.*
- *Excellent swelling in solvents ranging from toluene to water*

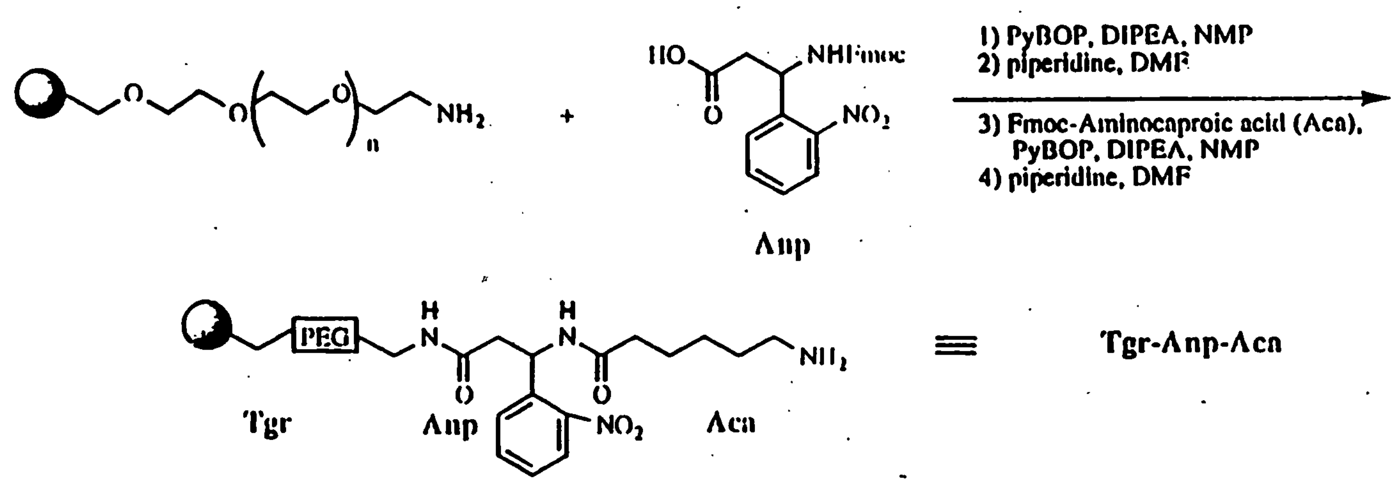


Figure 7

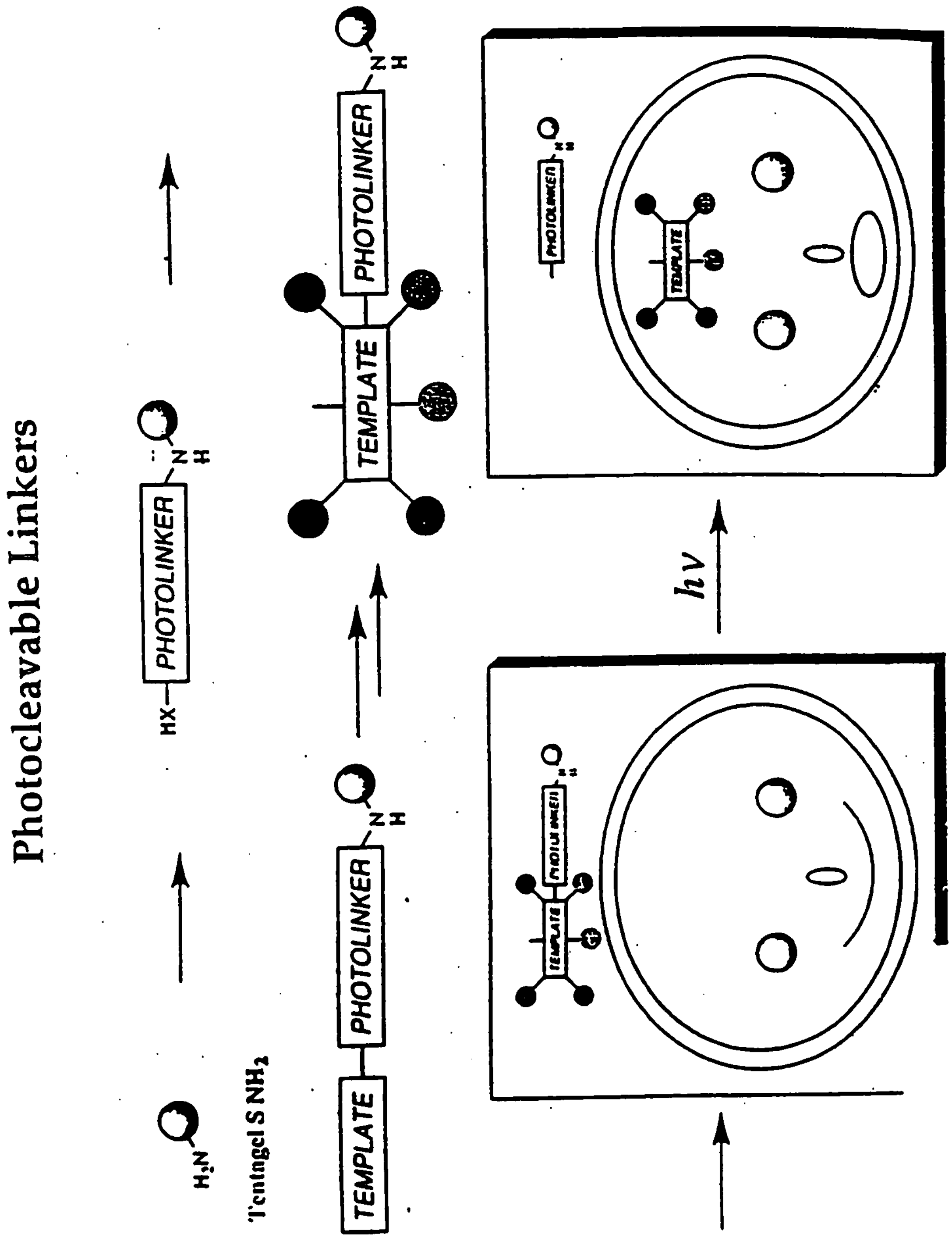
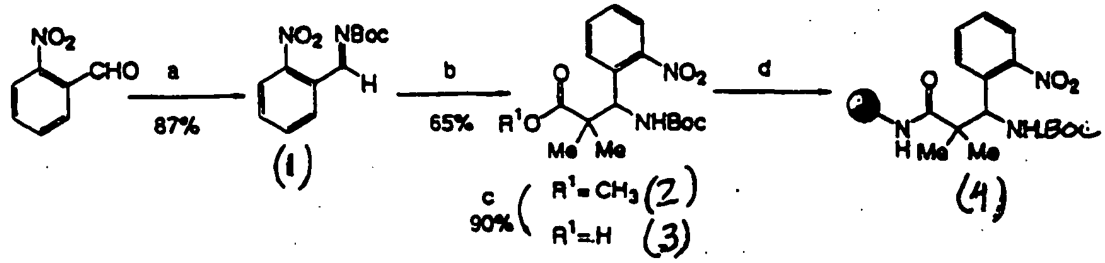

Photocleavable Linkers
H$_2$N
Tentagel S NH$_2$
HX
PHOTOLINKER
N H
TEMPLATE
PHOTOLINKER
TEMPLATE
PHOTOLINKER
hν
TEMPLATE
PHOTOLINKER
TEMPLATE
PHOTOLINKER

Figure 8

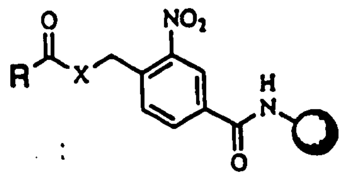
Synthesis of a novel ortho-nitrobenzyl photolabile linker



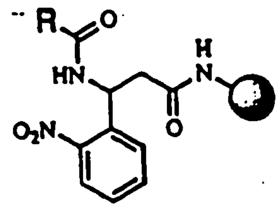
(a) i. *t*-BuOCONH$_2$ (1.5 eq.), NaSO$_2$Ph (2.5 eq.), HCOOH (2 eq.), 2:1 H$_2$O/MeOH, 3 crops over 60 h; ii. K$_2$CO$_3$, THF, reflux 12 h; (b) i. *i*-Pr$_2$NH, BuLi, THF, -78 °C, then methyl isobutyrate, 30 min; ii. 3, -78 °C, 2 min, then AcOH/THF; (c) LiOH (10 eq.), MeOH/H$_2$O, 60 °C; (d) Tentagel S NH$_2$, 5 (1.8 eq.), HATU (1.5 eq.), *i*-Pr$_2$NEt (4 eq.), 3:1 DMF/CH$_2$Cl$_2$, 12 h.

Figure 9

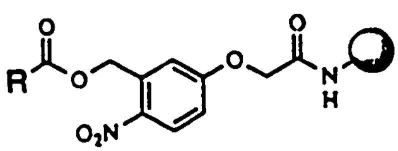
ortho-Nitrobenzyl Photolinkers



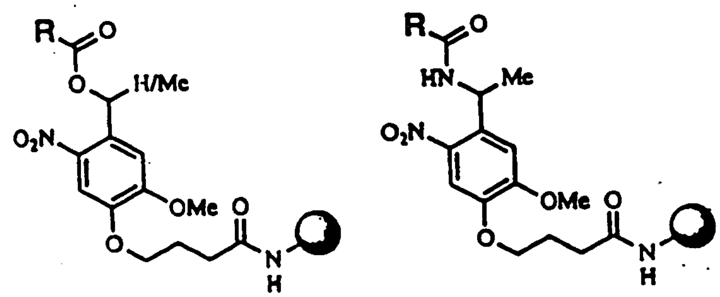
Rich Linker (Nba) 350 nm
Rich, Guwara
JACS, 1975, *97*, 1575.



Geysen Linker (Anp) 365 nm
Brown, Wagner, Geysen
Mol. Div., 1995, *1*, 4-12.



LINKER (A)



Affymax Linkers (Hep, Hmp, Aep) 365 nm
Holmes, Jones *JOC*, 1995, *60*, 2138;
Holmes *JOC*, 1997, *62*, 2370-2380

Figure 10

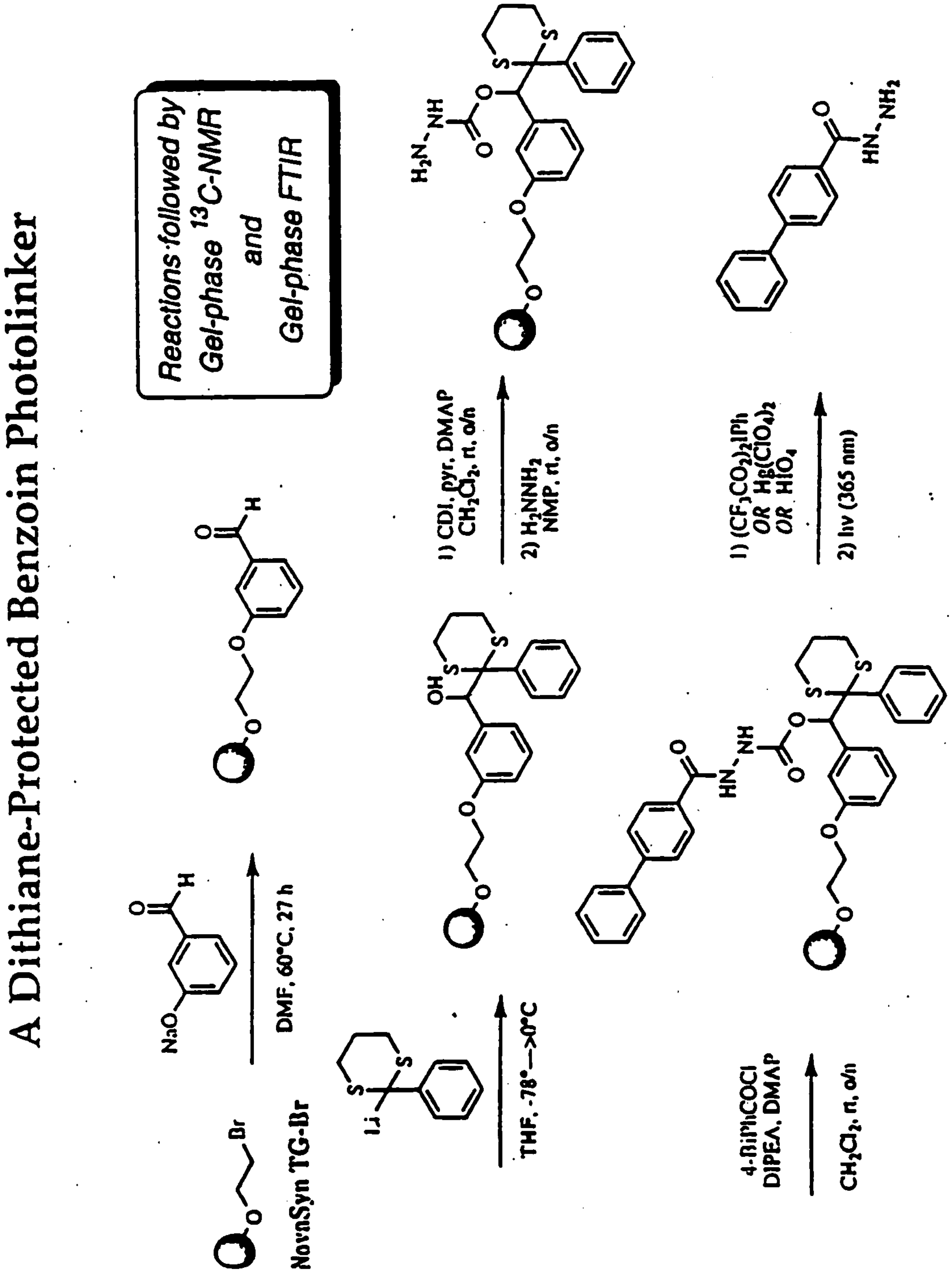

A Dithiane-Protected Benzoin Photolinker
Reactions followed by Gel-phase ^{13}C-NMR and Gel-phase FTIR
NovaSyn TG-Br
NaO
DMF, 60°C, 27 h
THF, -78° —>0°C
1) CDI, pyr, DMAP CH_2Cl_2, rt, o/n
2) H_2NNH_2 NMP, rt, o/n
4-BiPhCOCl DIPEA, DMAP
CH_2Cl_2, rt, o/n
1) $(CF_3CO_2)_2IPh$ OR $Hg(ClO_4)_2$ OR HIO_4
2) hv (365 nm)

Figure 11

Addition of an R_0 Diversity Position via Fukuyama Sulfonamide Alkylation

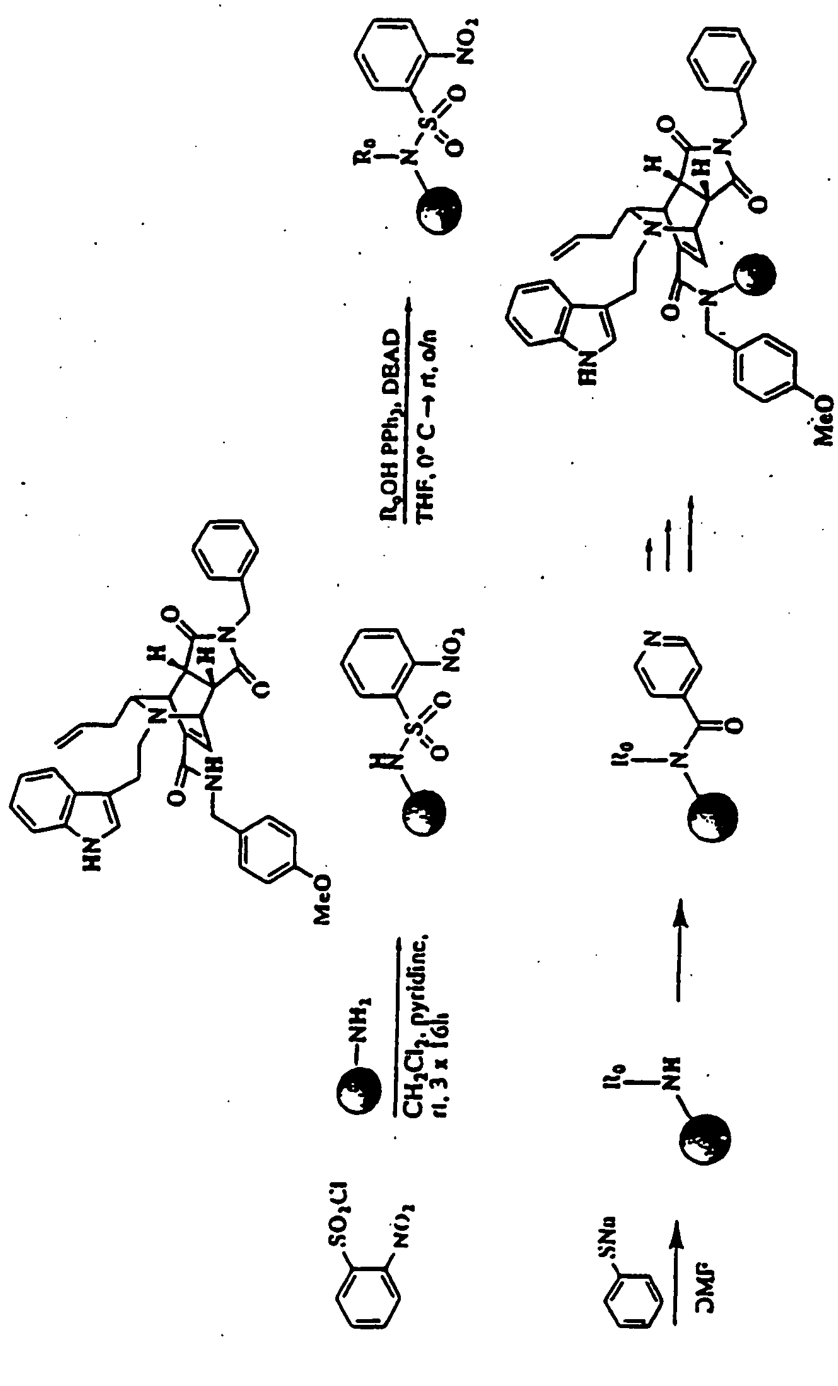
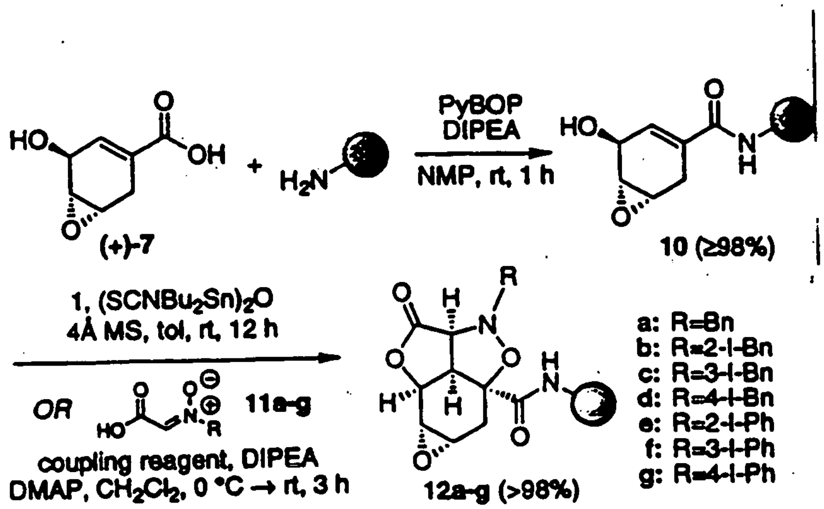


Figure 12



HO
OH
+
H_2N
PyBOP
DIPEA
NMP, rt, 1 h
(+)-7
10 (≥98%)
1, $(SCNBu_2Sn)_2O$
4Å MS, tol, rt, 12 h
OR
11a-g
coupling reagent, DIPEA
DMAP, CH_2Cl_2, 0 °C → rt, 3 h
12a-g (>98%)
a: R=Bn
b: R=2-I-Bn
c: R=3-I-Bn
d: R=4-I-Bn
e: R=2-I-Ph
f: R=3-I-Ph
g: R=4-I-Ph

Figure 13

Rapid Synthesis of Iodophenyl Nitrones

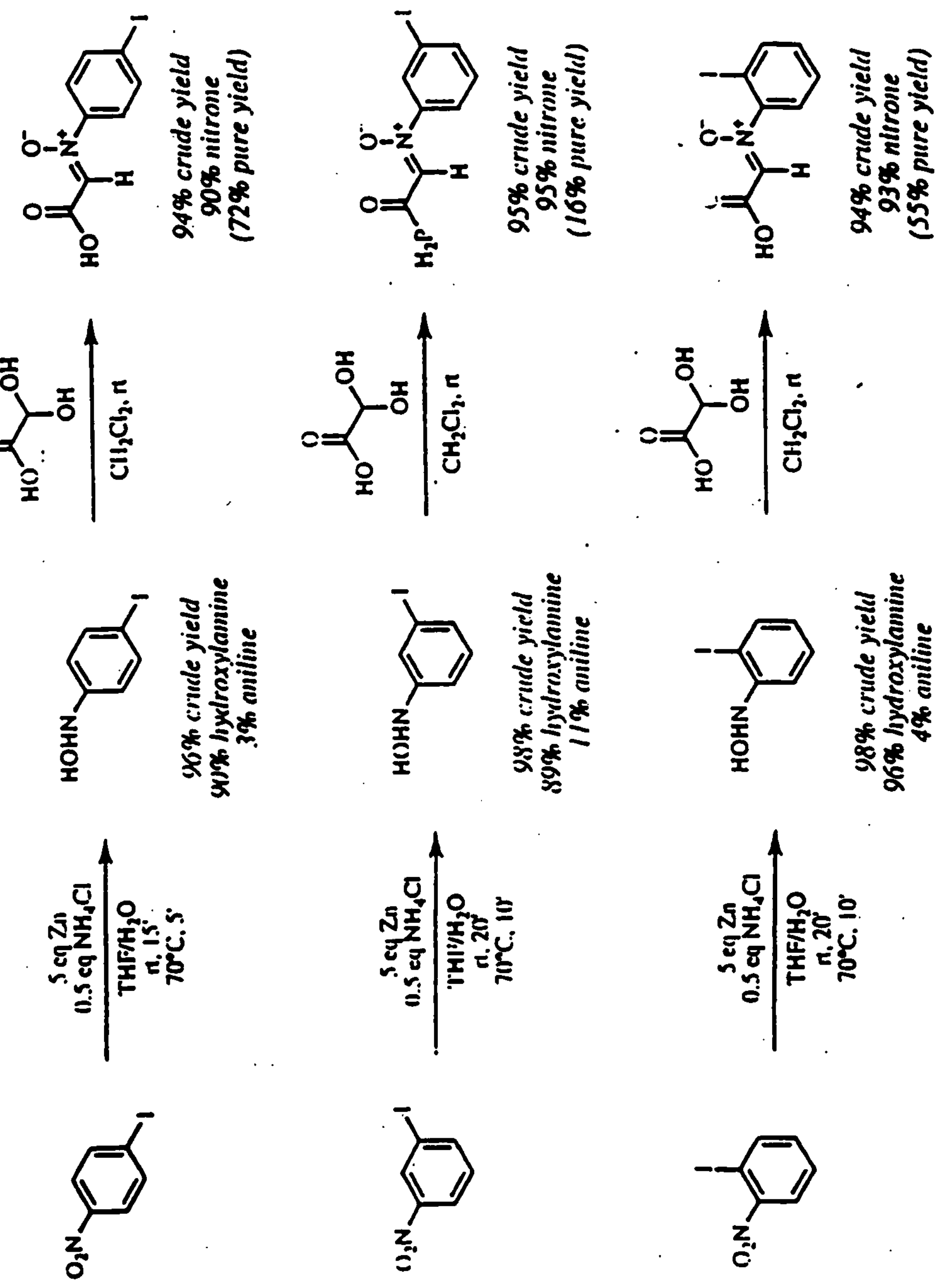


Figure 14

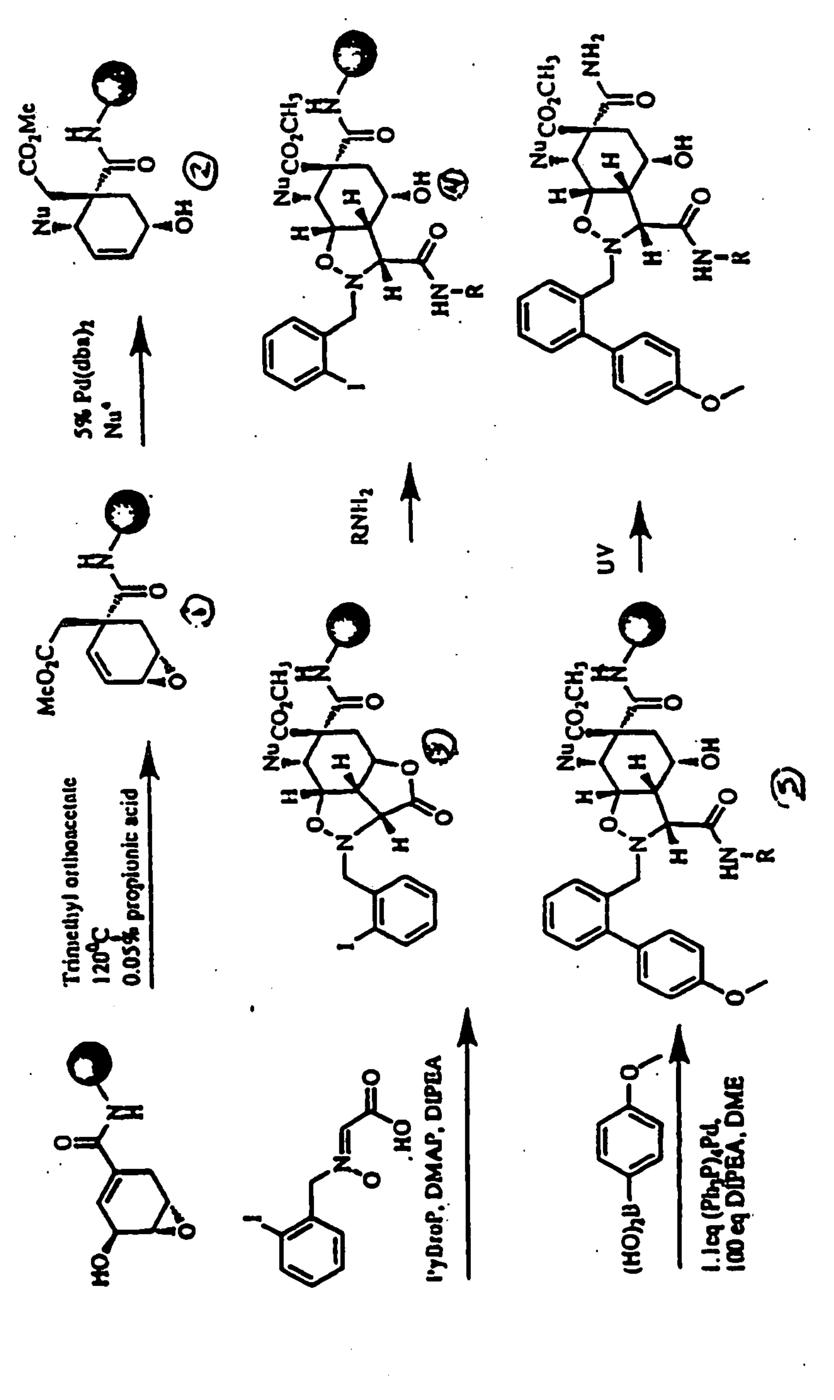

Trimethyl orthoacetate
120°C
0.05% propionic acid
5% Pd(dba)2
Nu
RNH2
UV
PyBroP, DMAP, DIPEA
1.1eq (Ph3P)4Pd,
100 eq DIPEA, DME

Figure 15

Acetoacetate as a Synthetic Intermediate

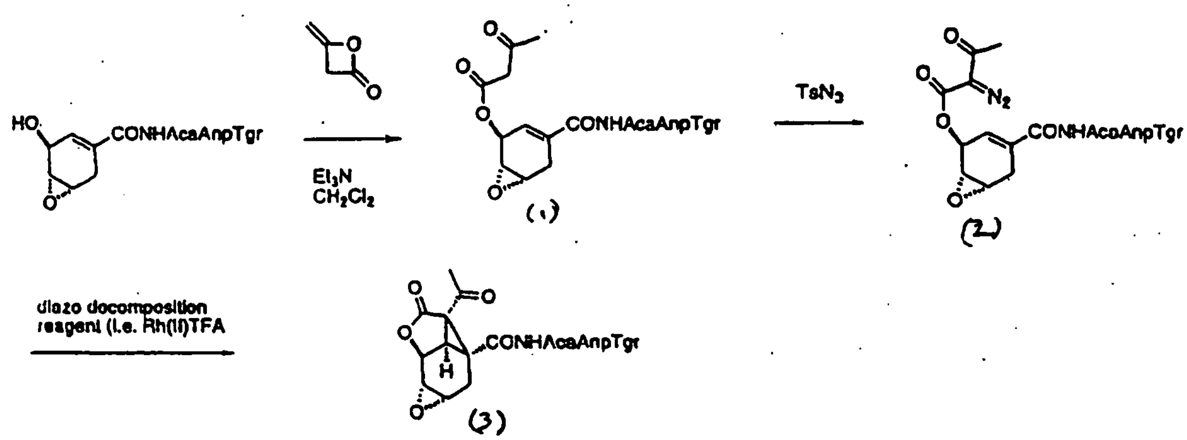
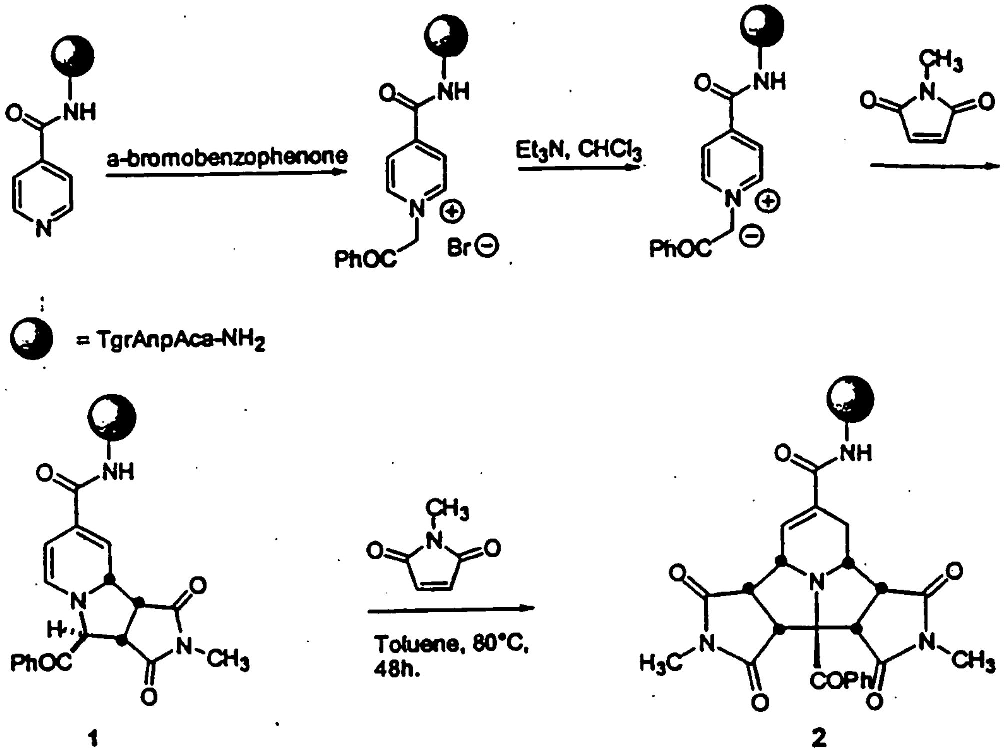


Figure 16



a-bromobenzophenone
Et3N, CHCl3
= TgrAnpAca-NH2
Toluene, 80°C, 48h.
1
2

Figure 17

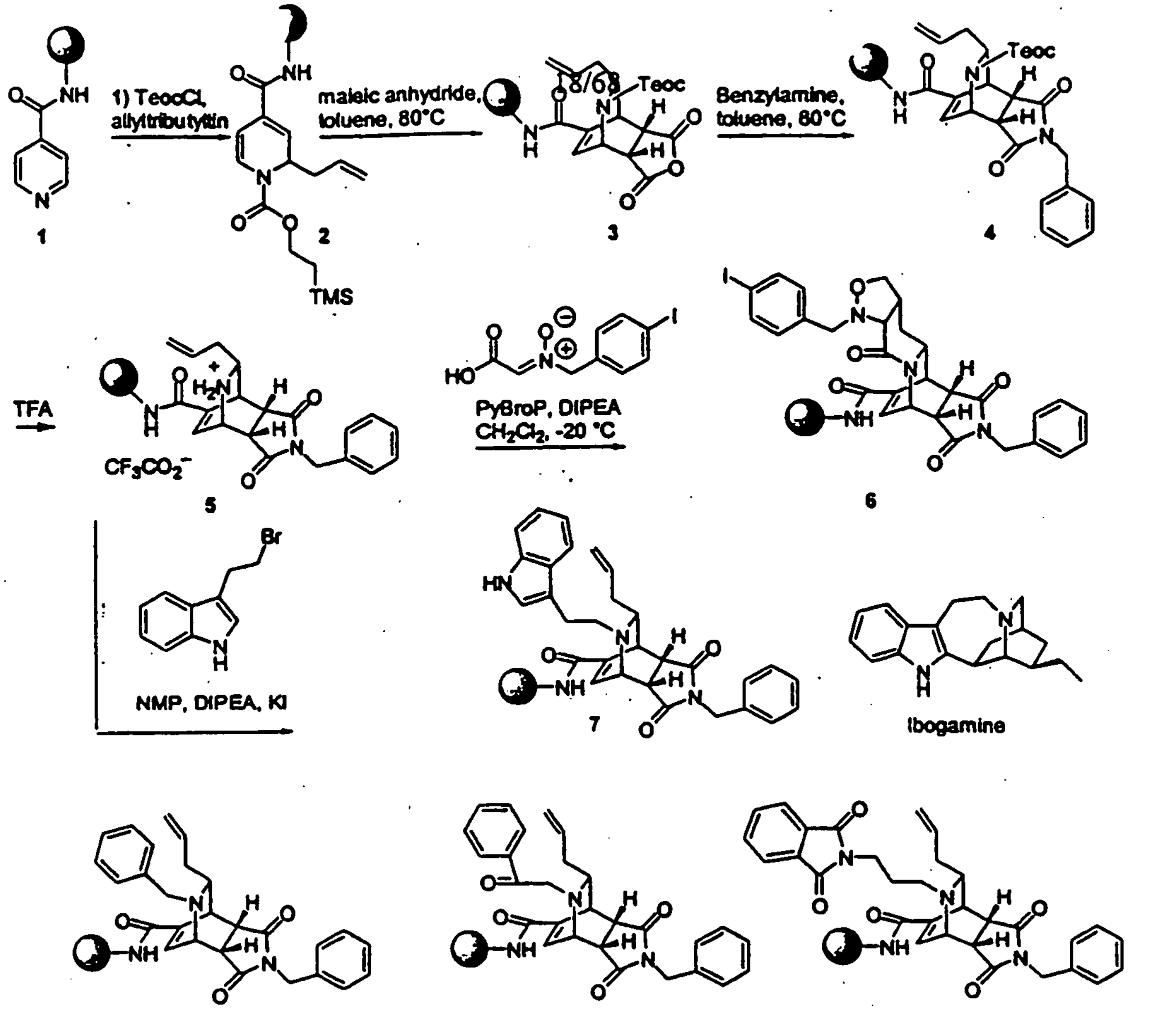

1) TeocCl, allyltributyltin
maleic anhydride, toluene, 80°C
Benzylamine, toluene, 80°C
TFA
PyBroP, DIPEA
CH_2Cl_2, -20 °C
NMP, DIPEA, KI
Ibogamine
TMS
Teoc
$CF_3CO_2^-$

Figure 18

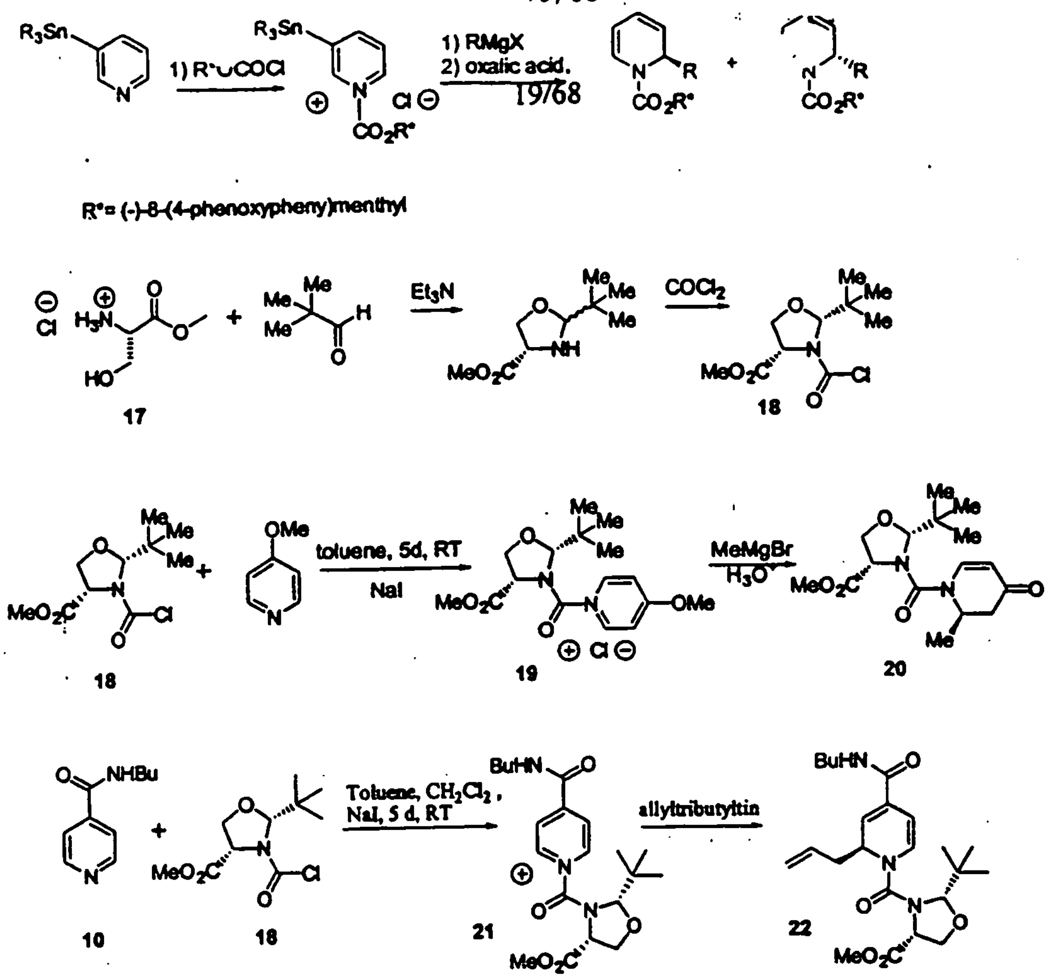
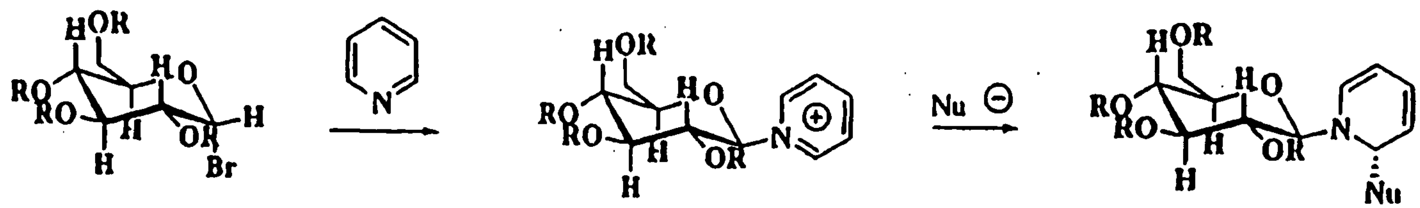

1) R*OCOCl
1) RMgX
2) oxalic acid.
R* = (-)-8-(4-phenoxypheny)menthyl
Et3N
COCl2
17
18
toluene, 5d, RT
NaI
MeMgBr
H3O+
19
20
Toluene, CH2Cl2,
NaI, 5 d, RT
allyltributyltin
10
18
21
22

Figure 19

Sugar Based Chiral Auxillary for the Synthesis of 1,2-dihydropyridines



(C. Marazano et al, Tet. Lett., 1990, 14, 1995-1998)

Figure 20

Photolytic Cleavage Reveals a Novel Rearrangement

Cleavage from the solid phase under UV conditions (354nm) causes photochemical rearrangement of the allyl functionality.

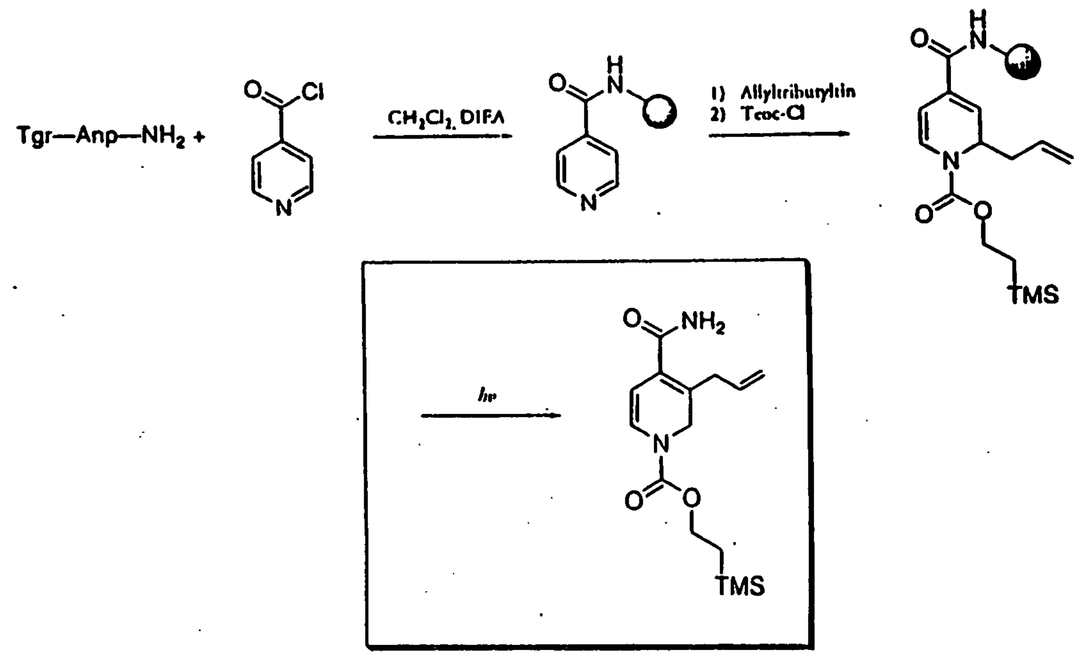


Figure 21

Solid-phase Cycloaddition Chemistry

Diels-Alder reactions under mild conditions produce rigid conformations in near-quantitative yields.

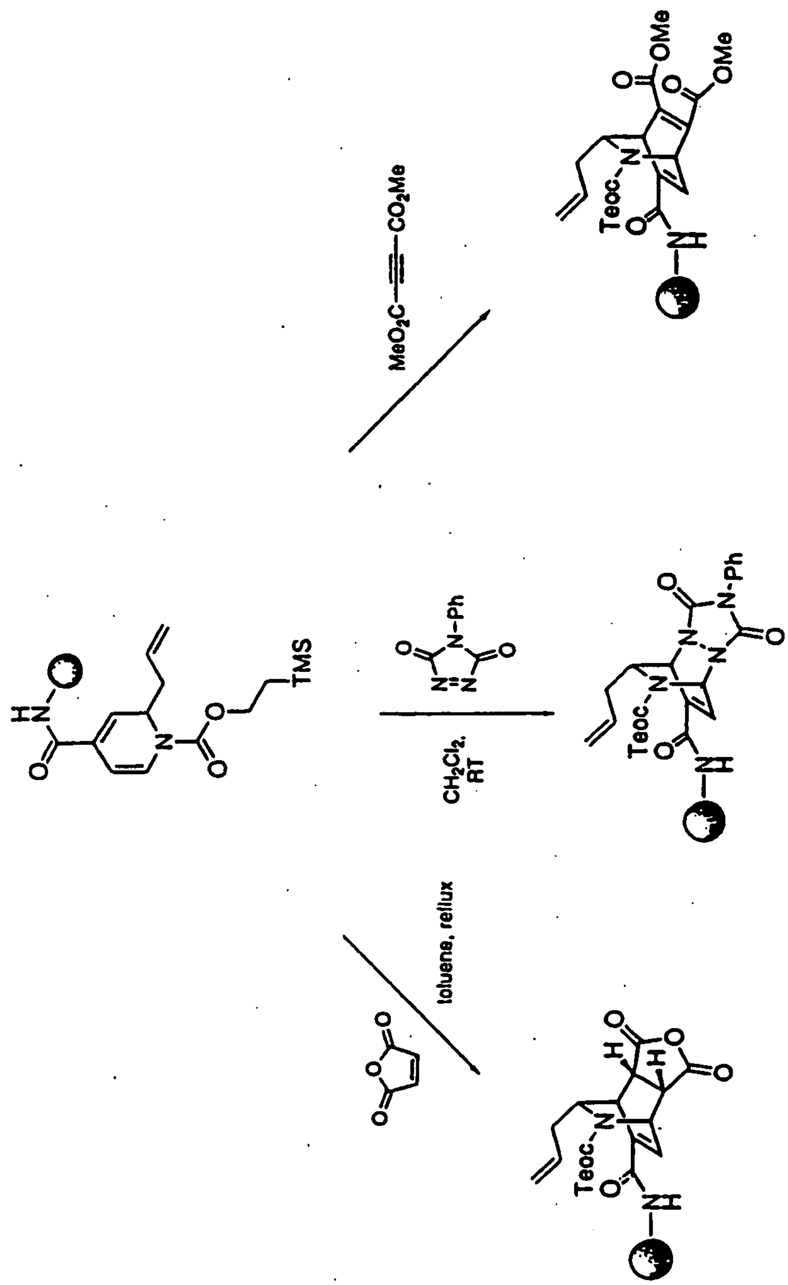


Figure 22

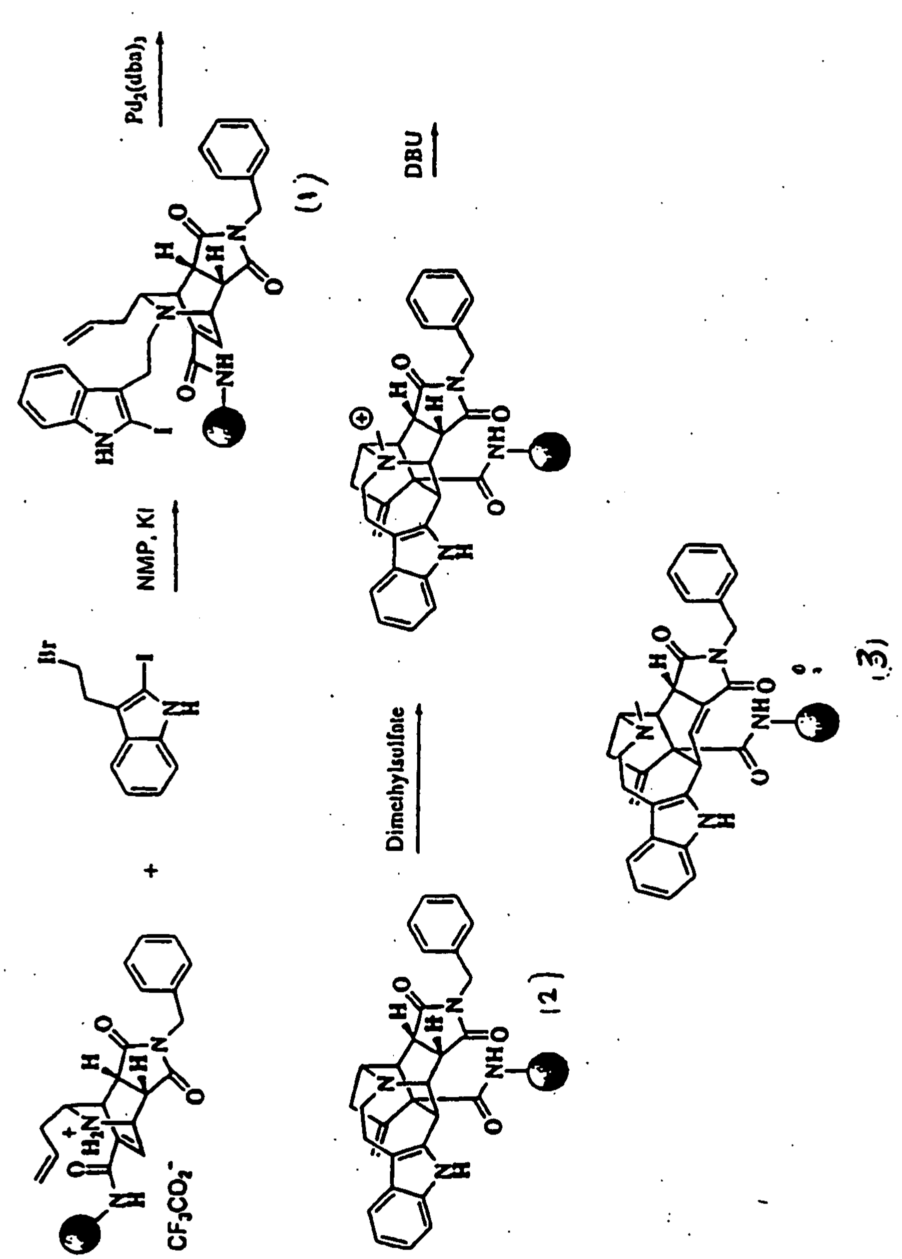


Figure 23

Solution Phase Lactone Aminolysis

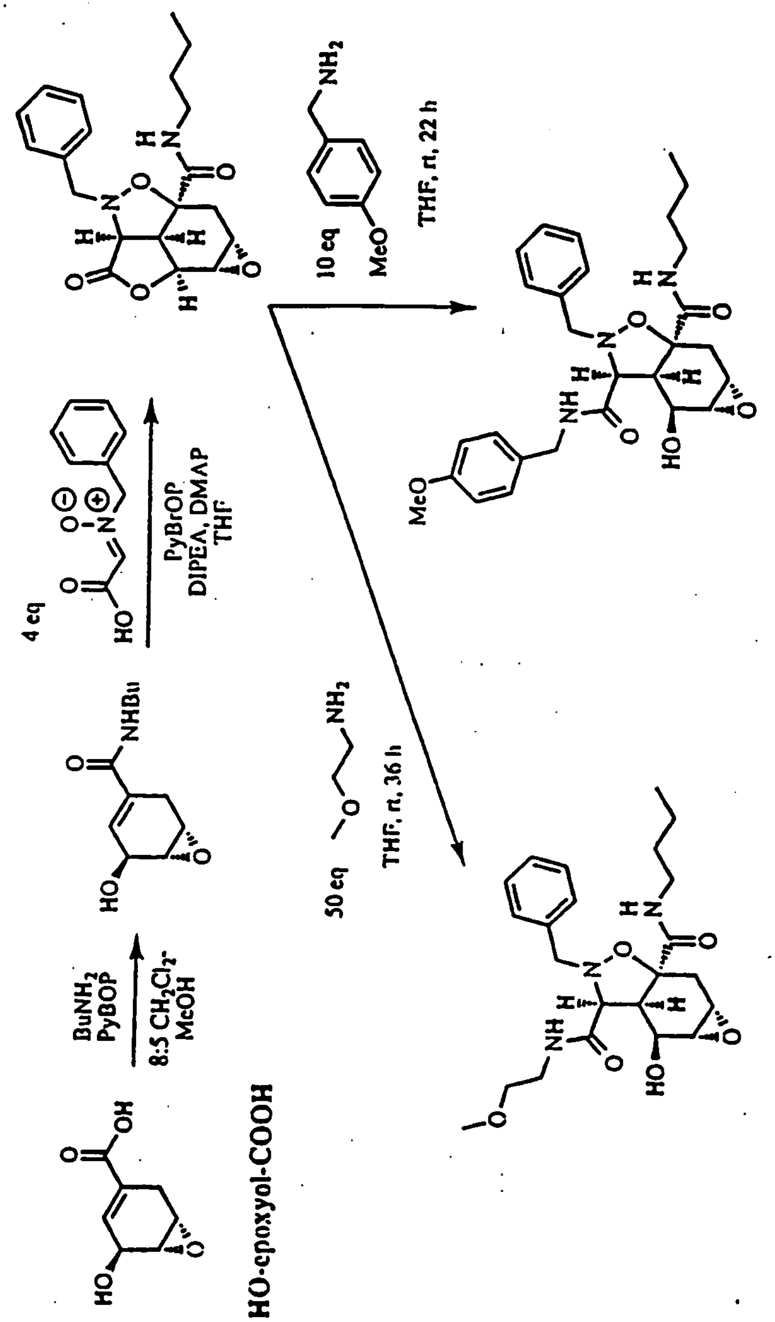


Figure 24

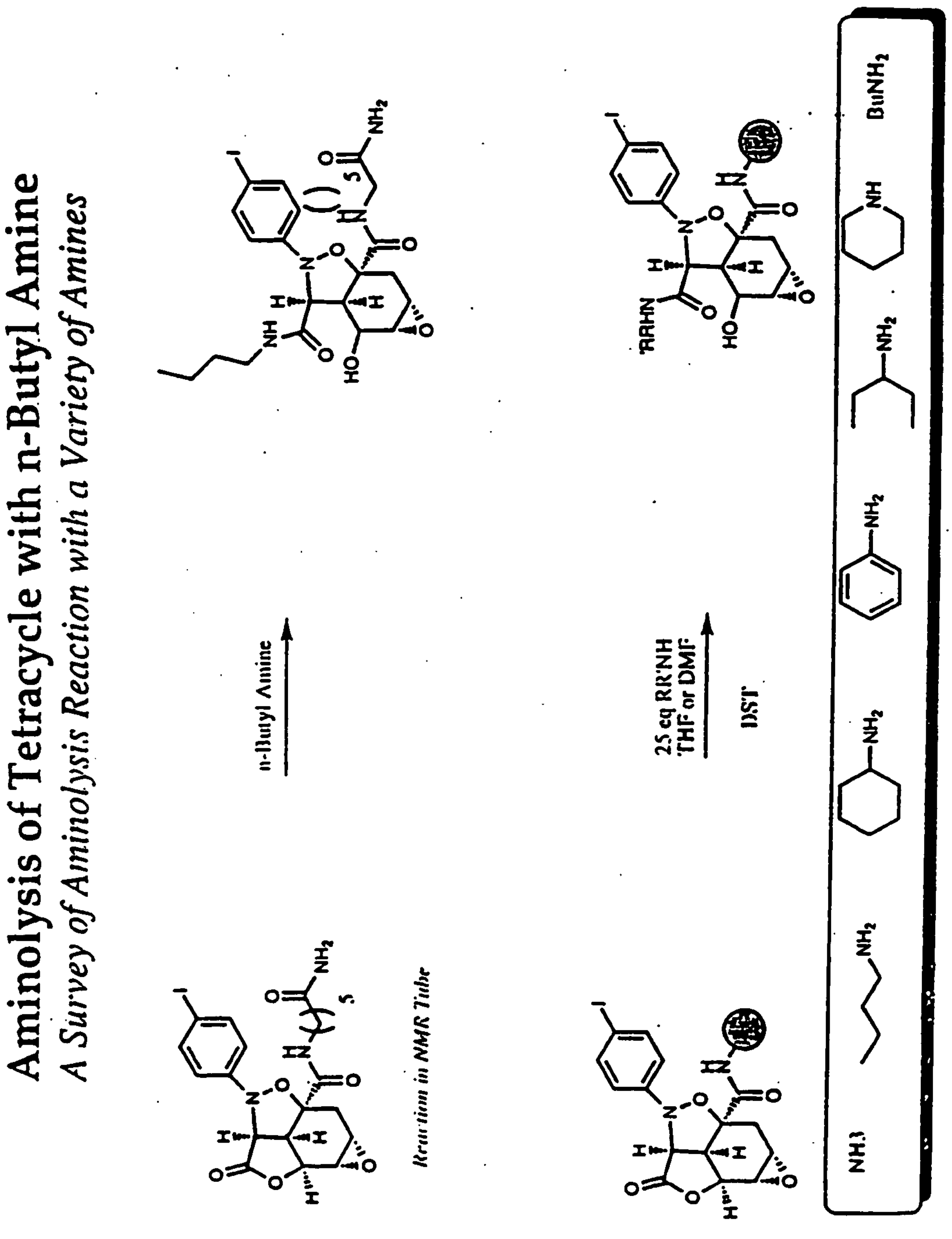

Aminolysis of Tetracycle with n-Butyl Amine
A Survey of Aminolysis Reaction with a Variety of Amines
n-Butyl Amine
Reaction in NMR Tube
25 eq RR'NH
THF or DMF
RT
NH3
BuNH2

Figure 25

2-Hydroxypyridine-Catalyzed Butyrolactone Aminolysis

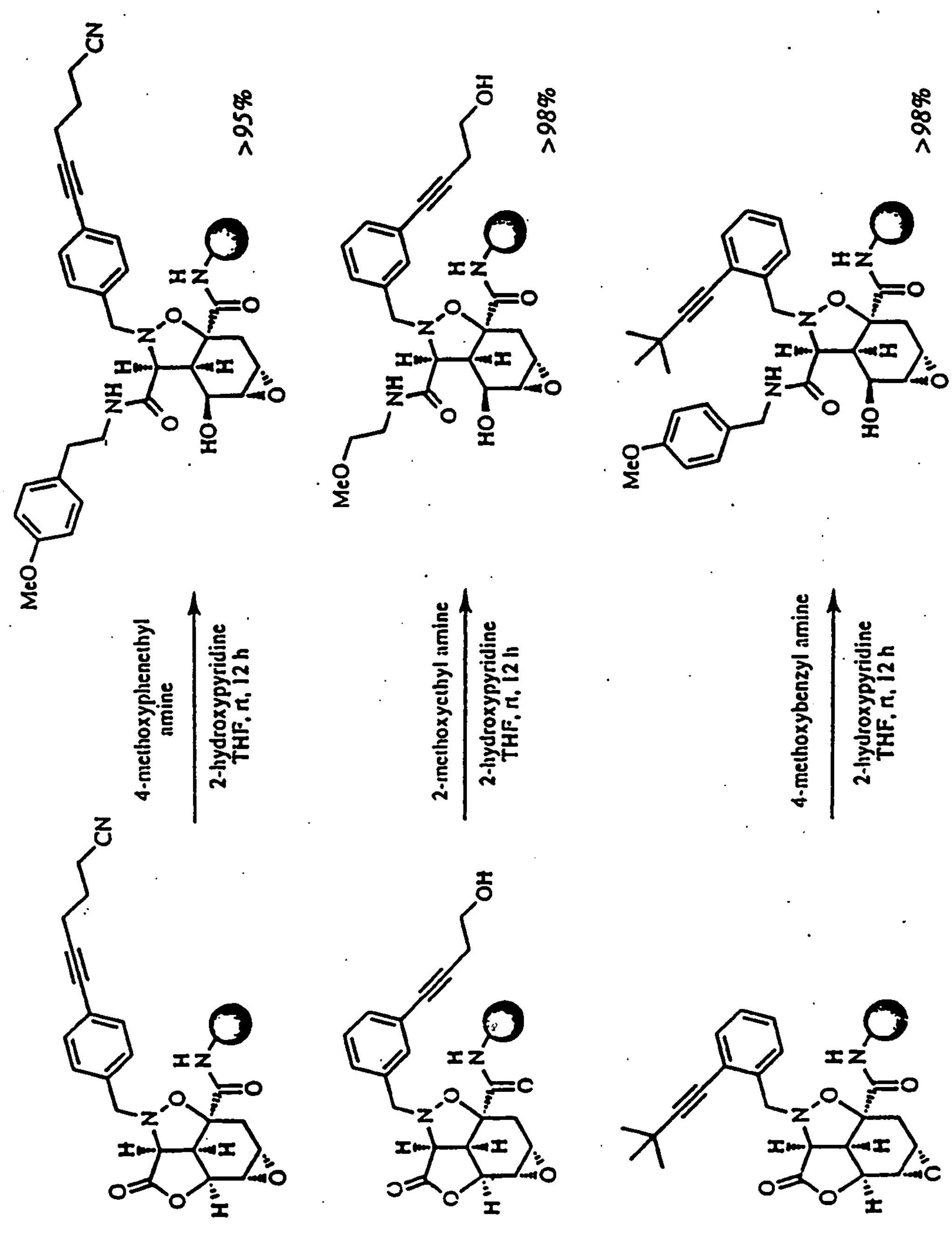


Figure 26

Acylation of the Unmasked Hydroxyamide

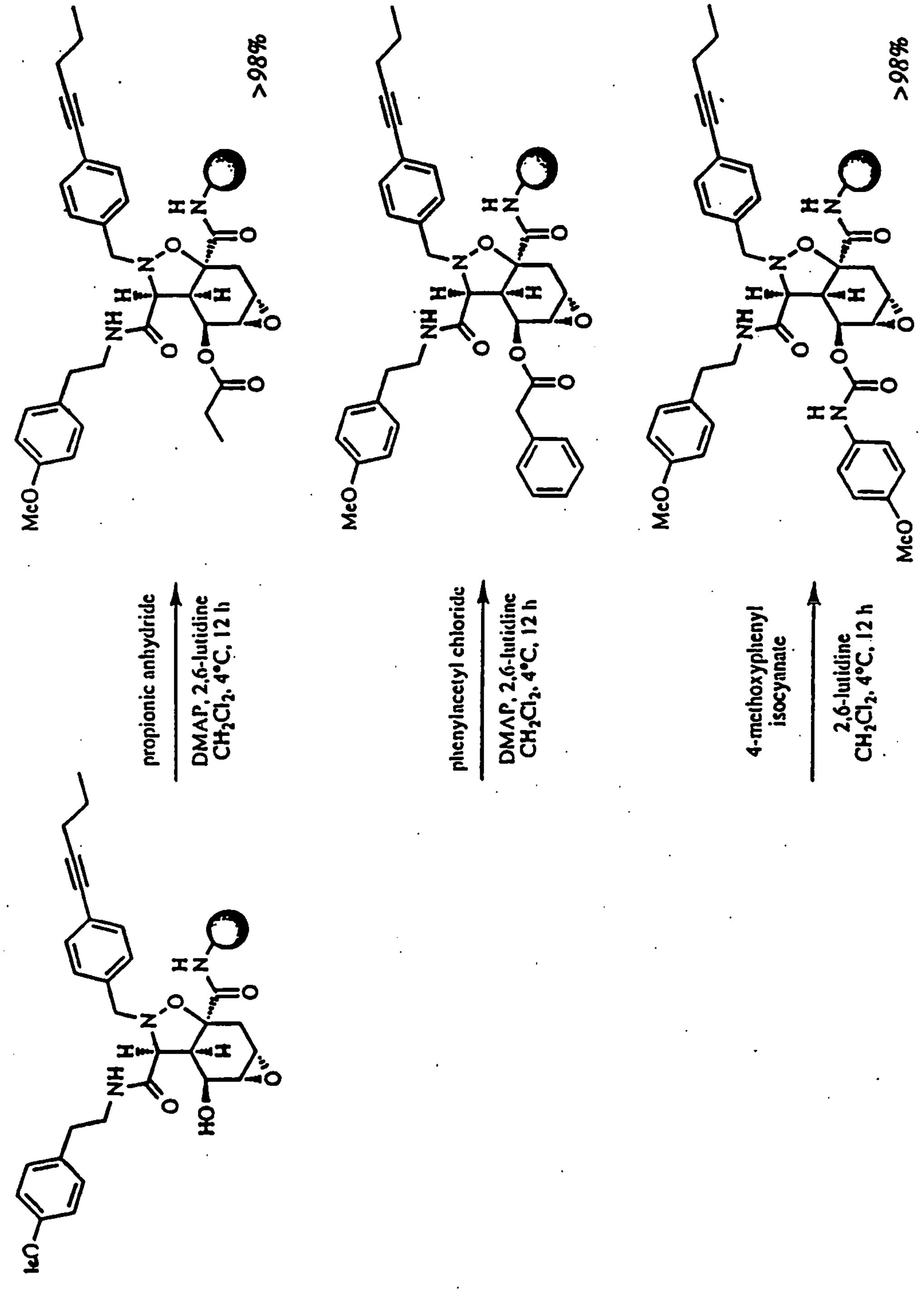
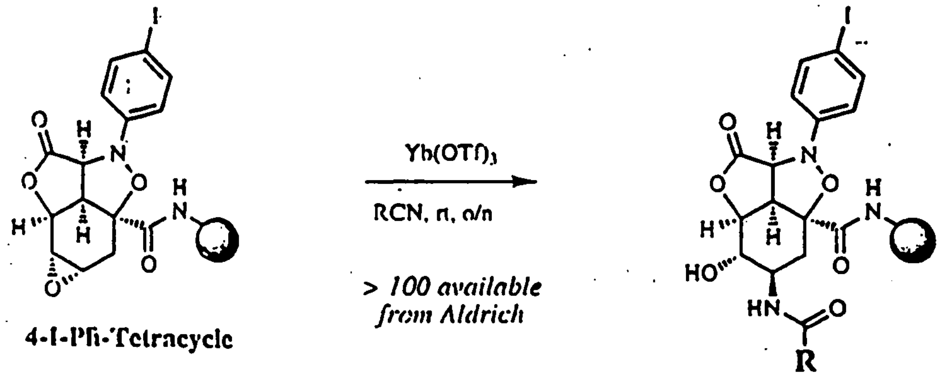


Figure 27

Epoxide Opening Reactions
Ytterbium triflate-catalyzed Ritter reaction



R = Me, Ph
clean product

Figure 28

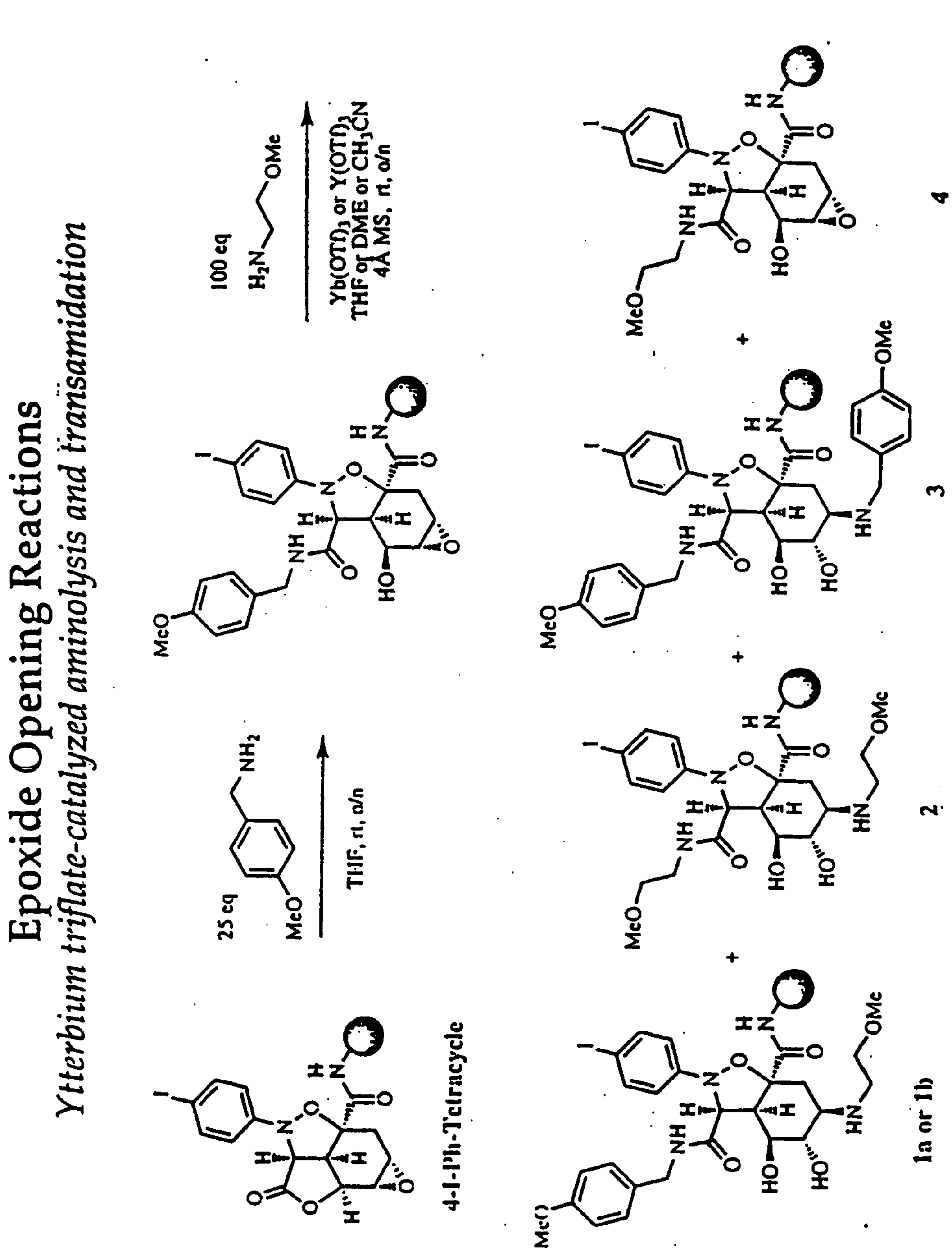
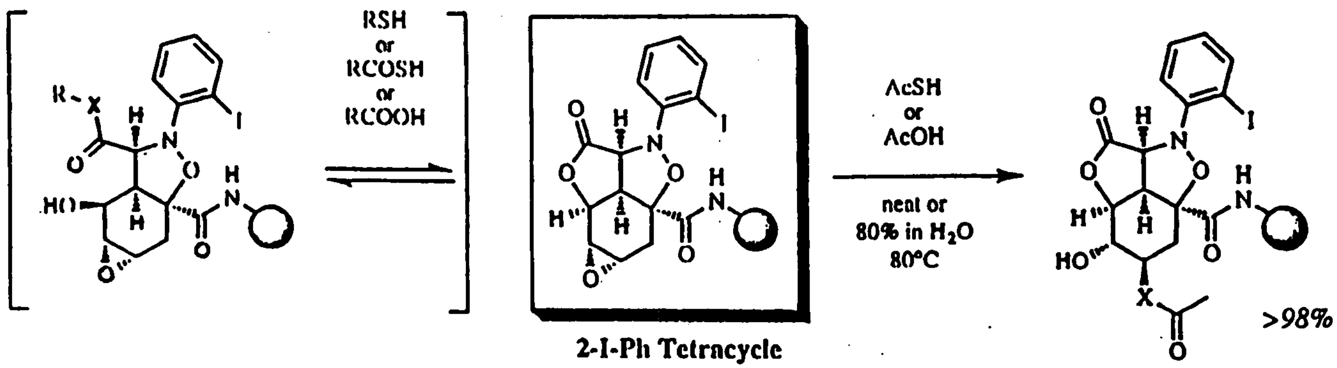

Epoxide Opening Reactions
Ytterbium triflate-catalyzed aminolysis and transamidation
4-I-Ph-Tetracycle
25 eq
THF, rt, o/n
100 eq
Yb(OTf)$_3$ or Y(OTf)$_3$
THF or DME or CH$_3$CN
4Å MS, rt, o/n
1a or 1b
2
3
4

Figure 29

A New/Old Epoxide Opening Reaction!!!

Chemoselective solvolysis with AcSH and AcOH



Epoxide solvolysis exposes hydroxyl and leaves an orthogonally protected thioacetate.

:Gowan, D. A.; Berchtold, G. A. *J. Org. Chem.* 1981, *46*, 2381-2383.

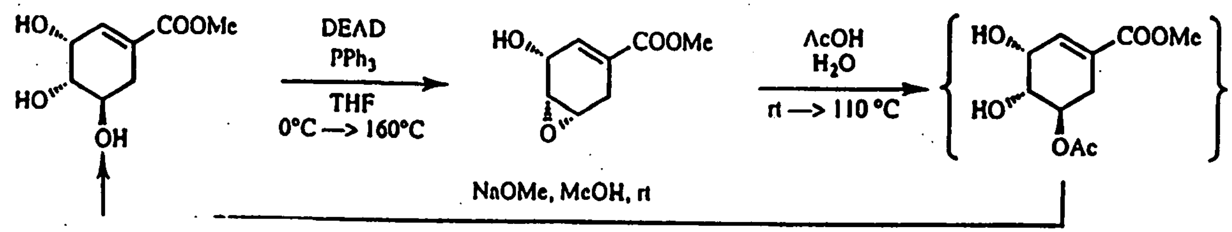


Figure 30

Epoxide Thiolysis

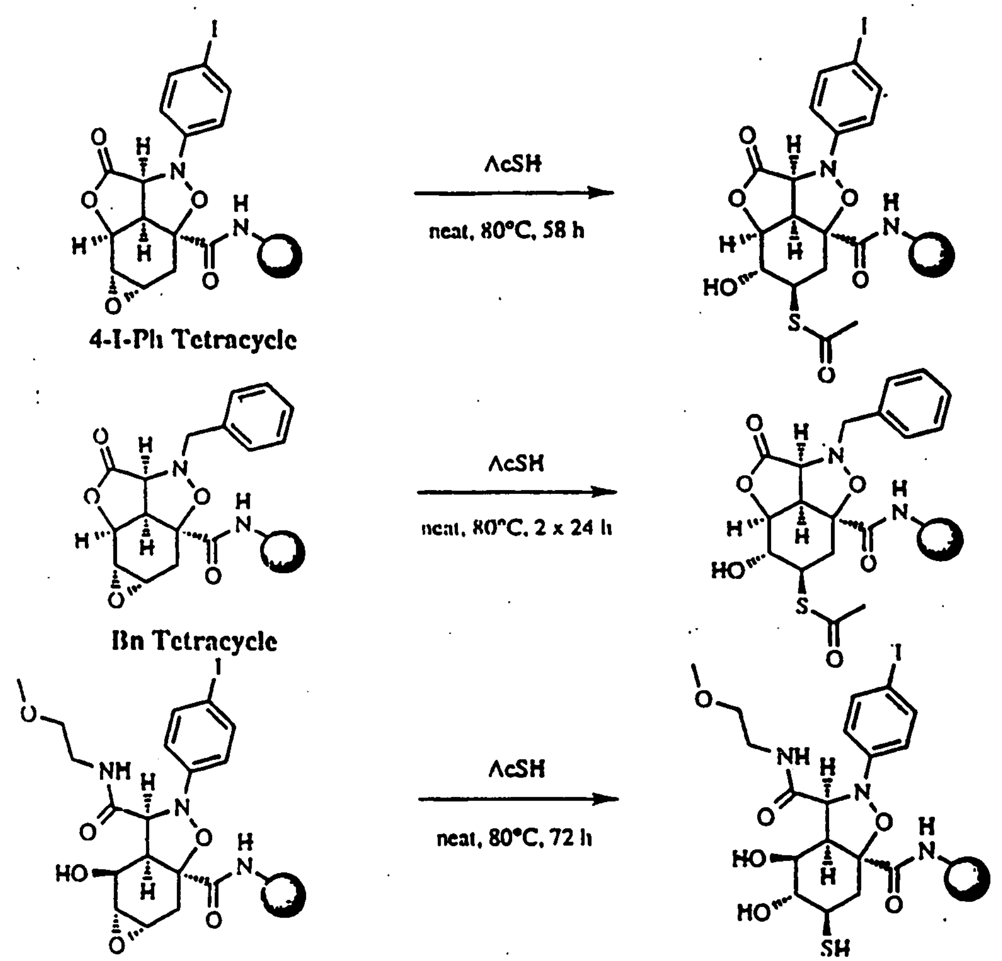


Figure 31

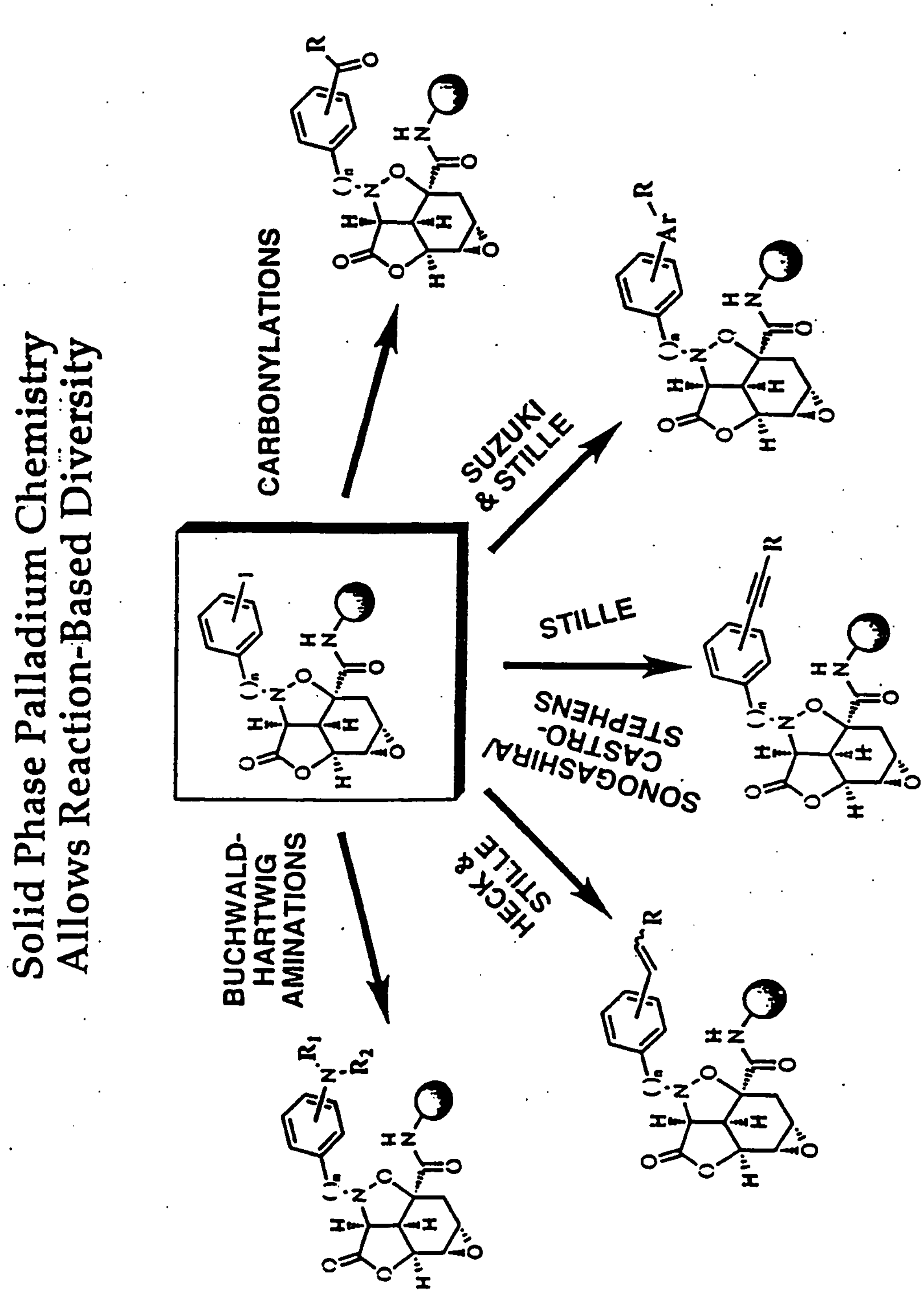

Solid Phase Palladium Chemistry
Allows Reaction-Based Diversity
CARBONYLATIONS
SUZUKI & STILLE
STILLE
SONOGASHIRA/ CASTRO-STEPHENS
HECK & STILLE
BUCHWALD-HARTWIG AMINATIONS

Figure 32

Palladium Cross-Coupling Reactions at the Aryl Iodide

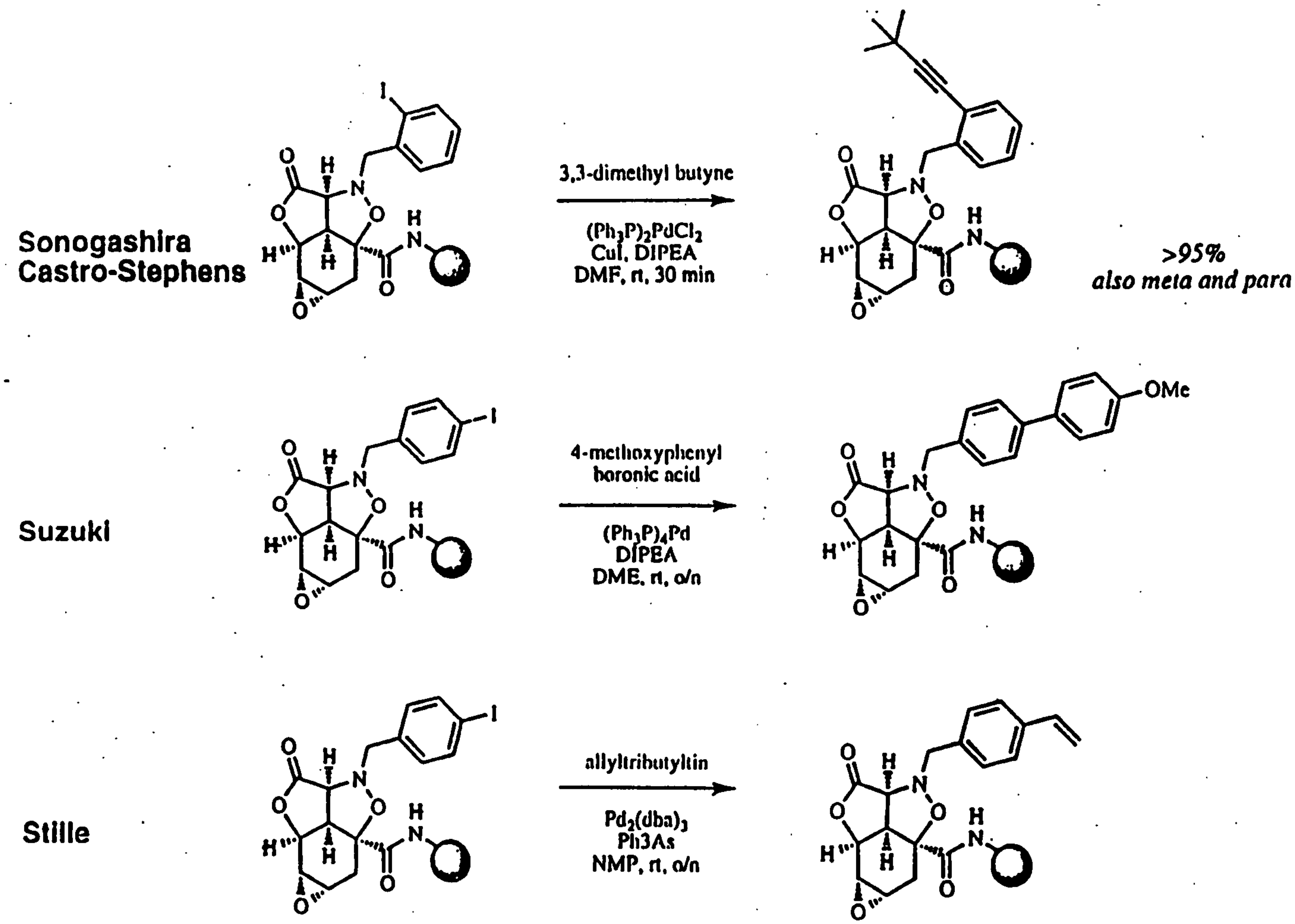


Figure 33

Rhodium-Catalyzed Hydroacylation and Azide Cycloaddition at the Aryl Alkyne

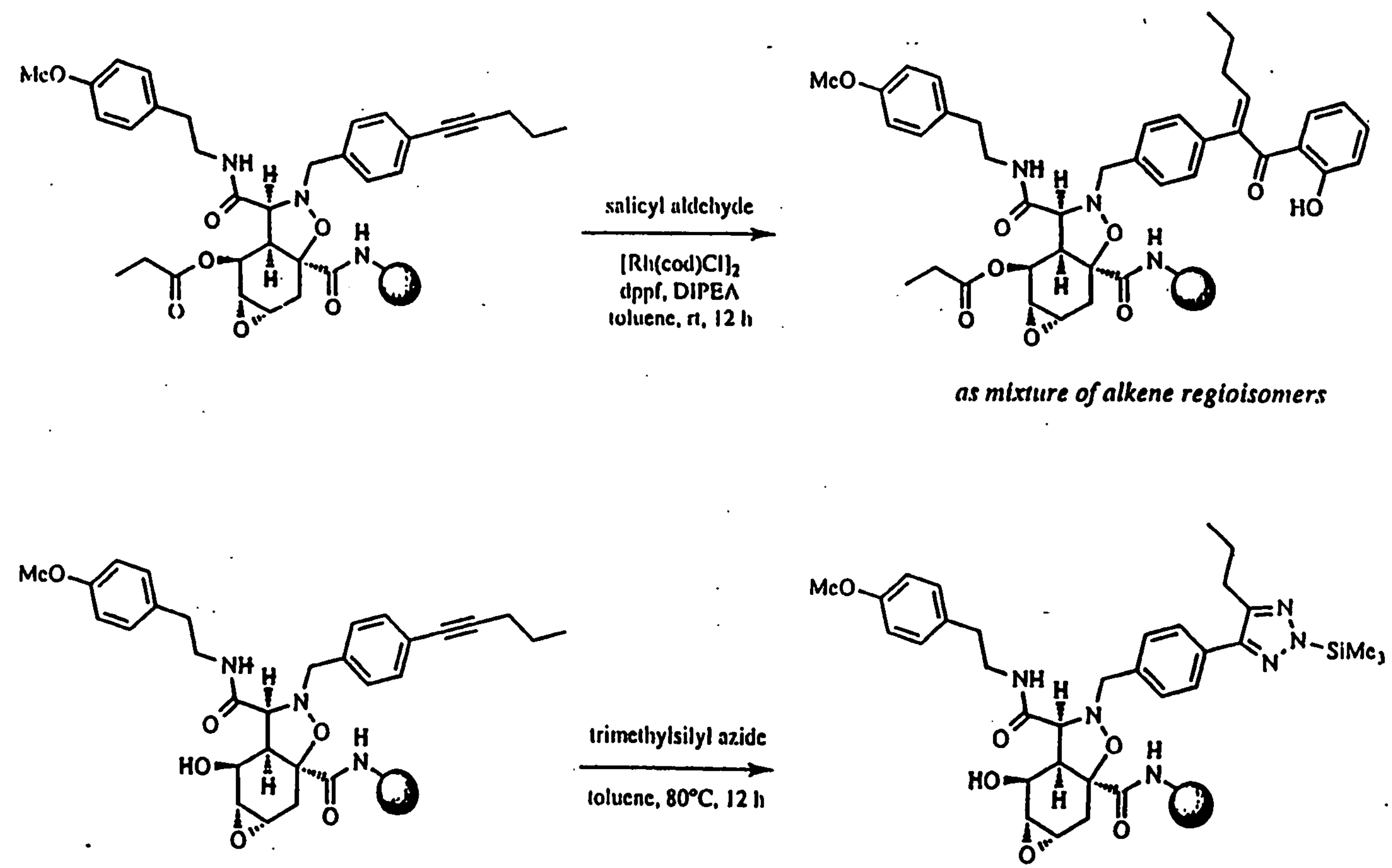


Figure 34

Nitrone and Nitrile Oxide, Alkyne Cycloadditions

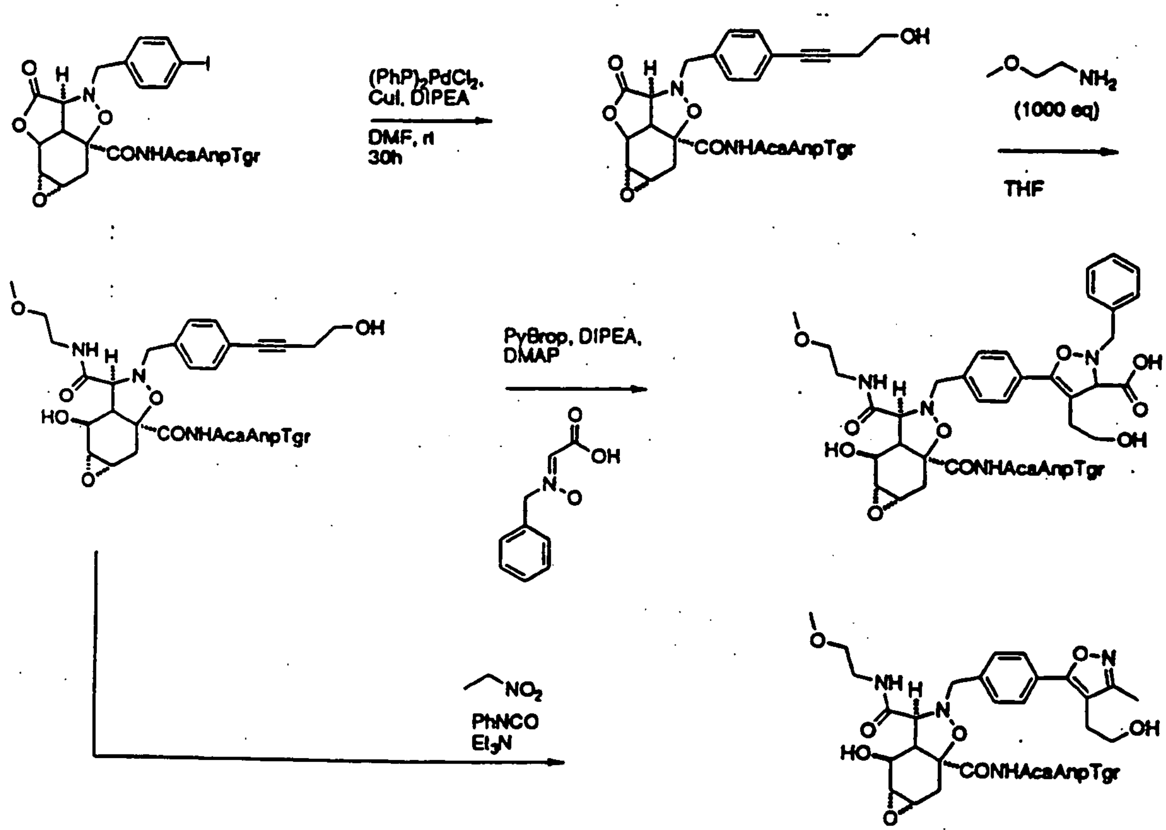
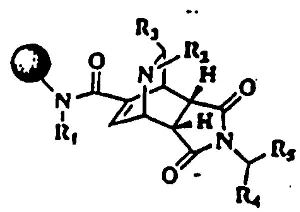


Figure 35

Representative Potential Nucleation Points



R_1= from aliphatic alcohols which will be attached by a Mitsunobu reaction. Straight chain, branched, and cyclic alcohol. The key requirement is that the alcohol not have an unprotected site that could be acylated. An amine, thiol etc.

R_2= Chloroformates (alcohols reacted with phosgene), and anything that can acylate or alkylate an amine. i.e. alkyl bromides, mesylates, aldehydes, etc...

R_3= allyl any allyl derivative of allyltributyltin, thiazole, indole

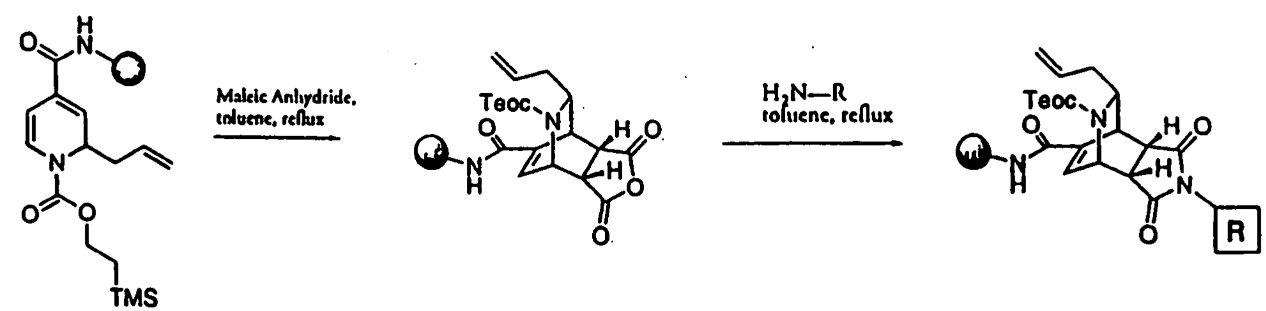
R_4= all amines and amino acids

R_5= all amines and alcohols

Figure 36

Efficient Synthesis of N-Arylimide Derivatives

3 positions provide multiple functionality. A wide variety of monomers can be accommodated, including amino acids.



N—R	Yield
Valine	98%
Valine-OMe	96%
Tryptophan	93%
Phenylalanine-OMe	94%
2-aminobenzoic acid	95%

Side chain extensions provide additional functionality

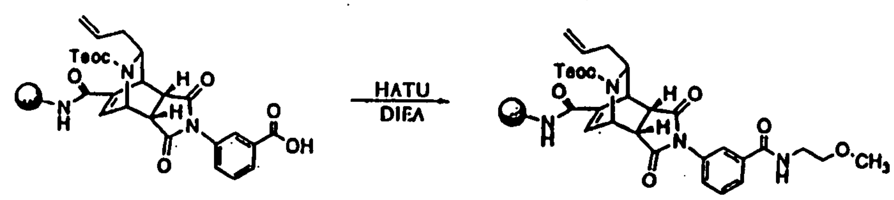


Figure 37

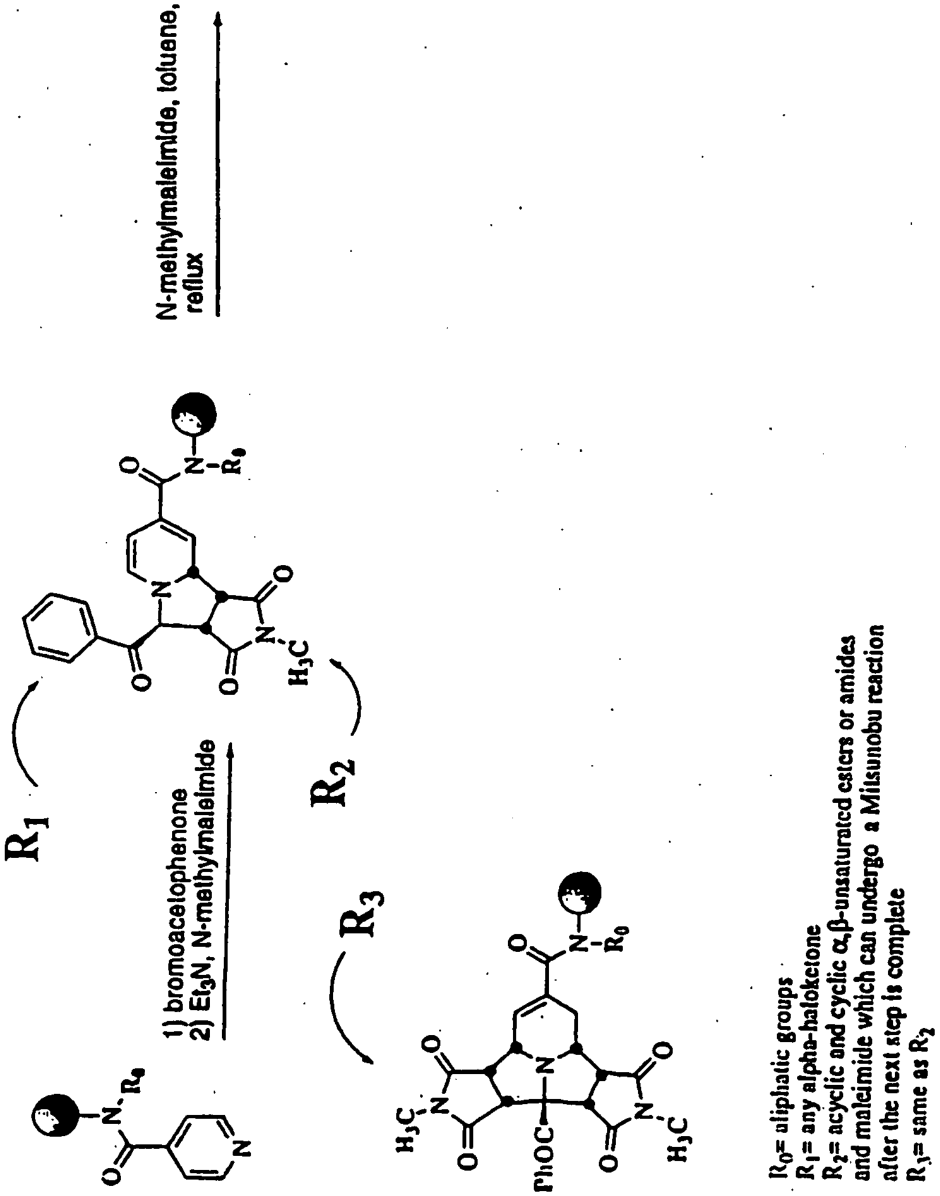

1) bromoacetophenone
2) Et3N, N-methylmaleimide
N-methylmaleimide, toluene, reflux
R1
R2
R3
R0= aliphatic groups
R1= any alpha-haloketone
R2= acyclic and cyclic α,β-unsaturated esters or amides and maleimide which can undergo a Mitsunobu reaction after the next step is complete
R3= same as R2

Figure 38

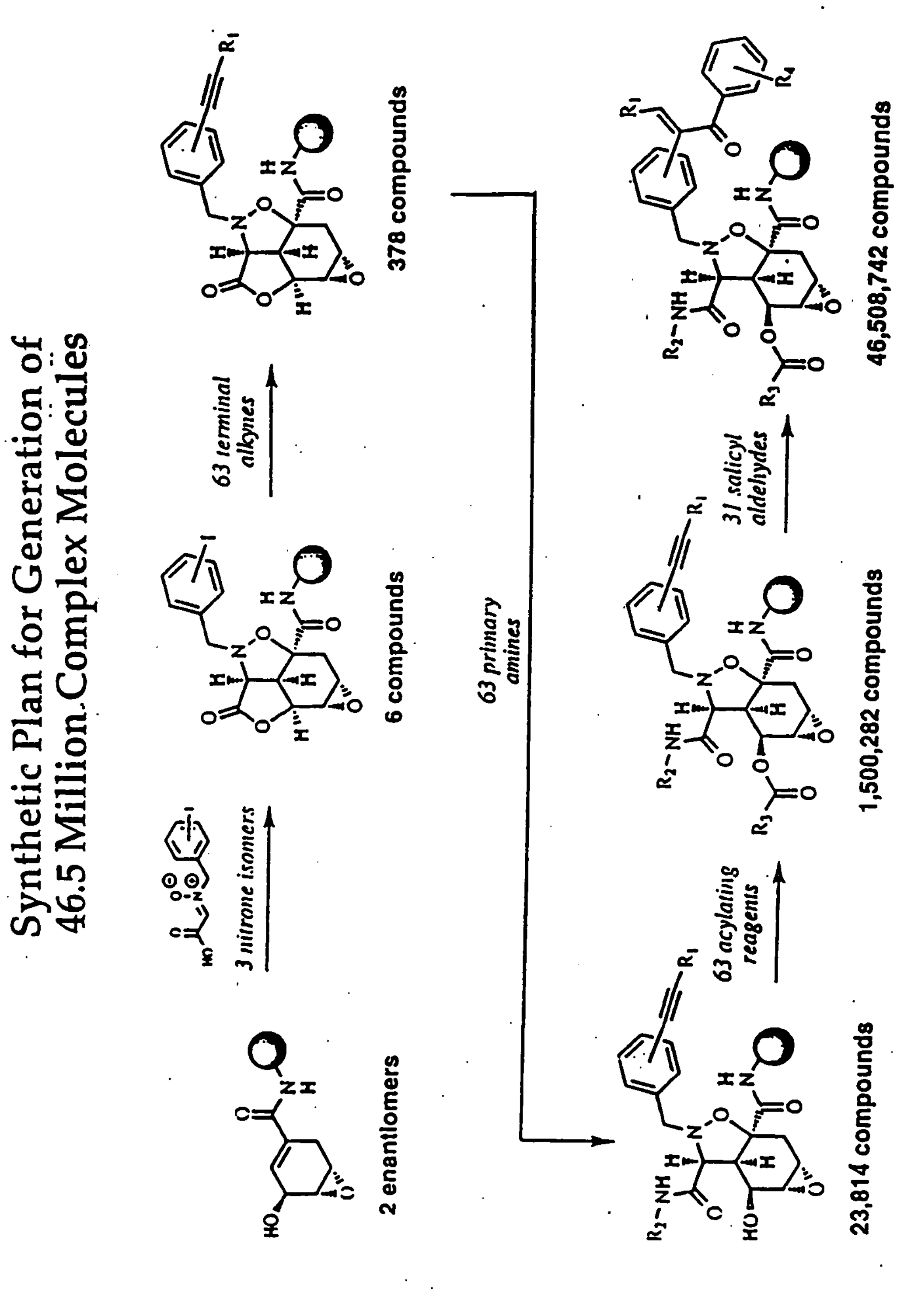

Synthetic Plan for Generation of
46.5 Million Complex Molecules
2 enantiomers
3 nitrone isomers
6 compounds
63 terminal alkynes
378 compounds
63 primary amines
23,814 compounds
63 acylating reagents
1,500,282 compounds
31 salicyl aldehydes
46,508,742 compounds

Figure 39

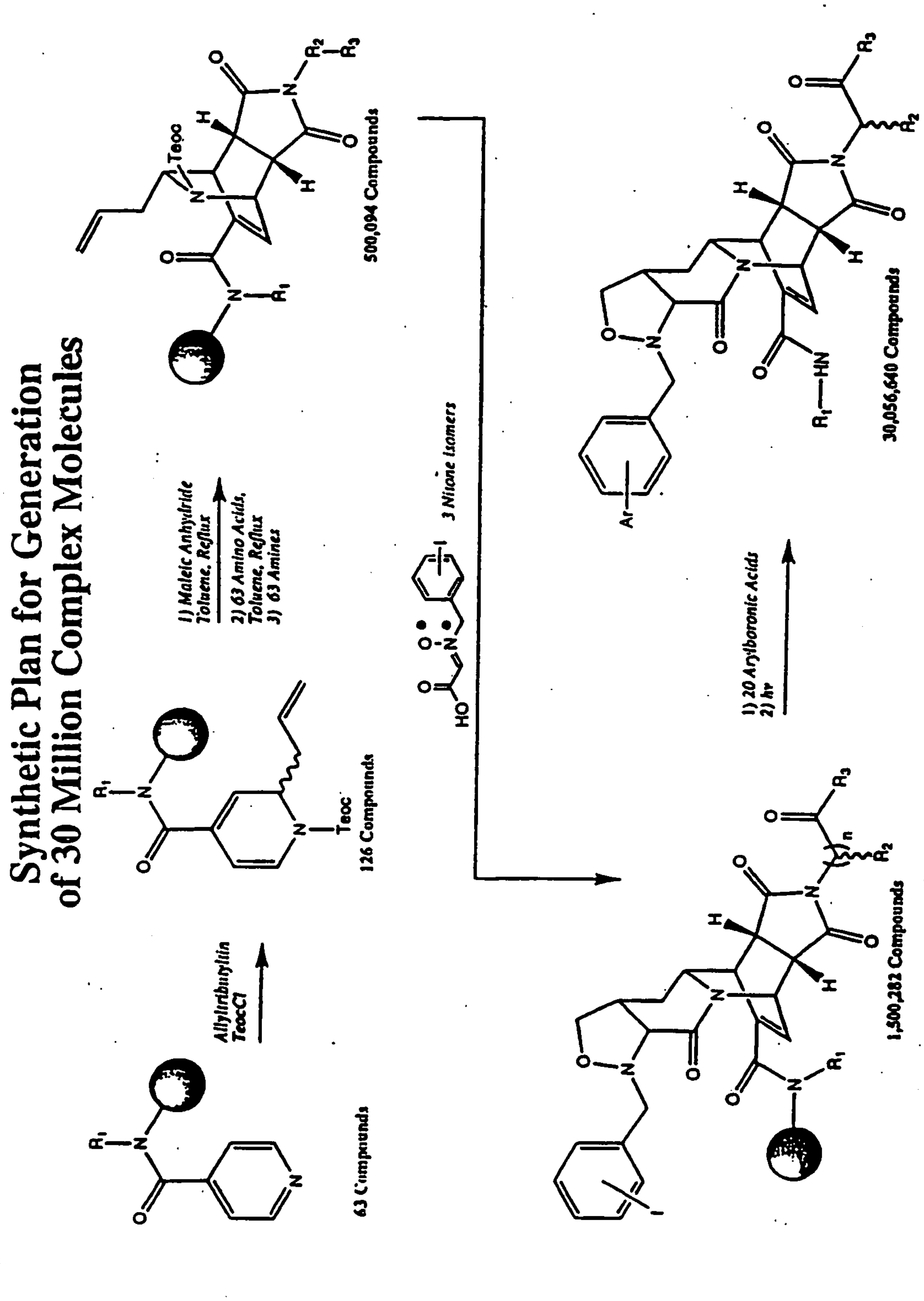

Synthetic Plan for Generation
of 30 Million Complex Molecules
63 Compounds
Allyltributyltin
TeocCl
126 Compounds
1) Maleic Anhydride
Toluene, Reflux
2) 63 Amino Acids,
Toluene, Reflux
3) 63 Amines
500,094 Compounds
3 Nitone Isomers
1,500,282 Compounds
1) 20 Arylboronic Acids
2) hν
30,056,640 Compounds

Figure 40

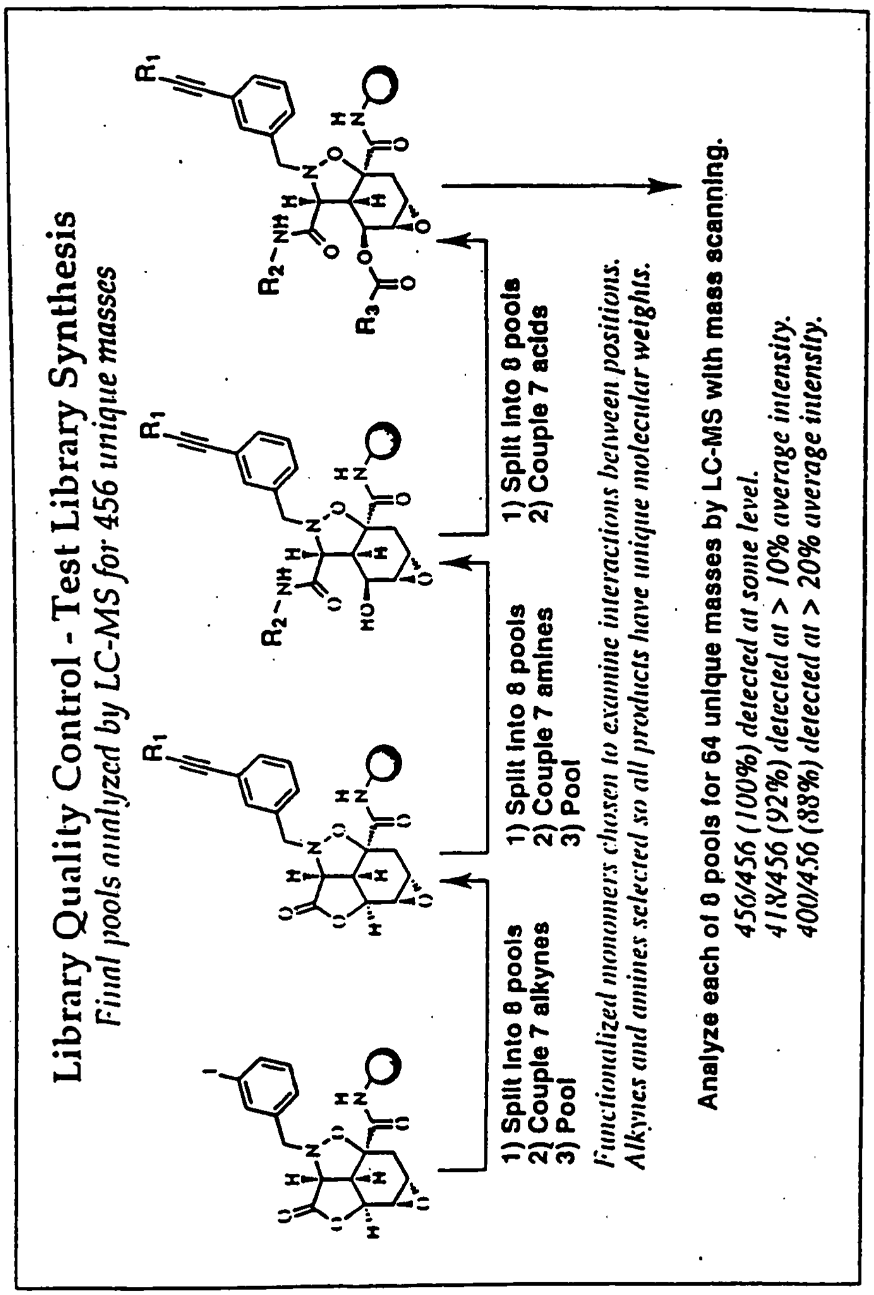

Library Quality Control - Test Library Synthesis
Final pools analyzed by LC-MS for 456 unique masses
1) Split into 8 pools
2) Couple 7 alkynes
3) Pool
1) Split into 8 pools
2) Couple 7 amines
3) Pool
1) Split into 8 pools
2) Couple 7 acids
Functionalized monomers chosen to examine interactions between positions.
Alkynes and amines selected so all products have unique molecular weights.
Analyze each of 8 pools for 64 unique masses by LC-MS with mass scanning.
456/456 (100%) detected at some level.
418/456 (92%) detected at > 10% average intensity.
400/456 (88%) detected at > 20% average intensity.

Figure 41

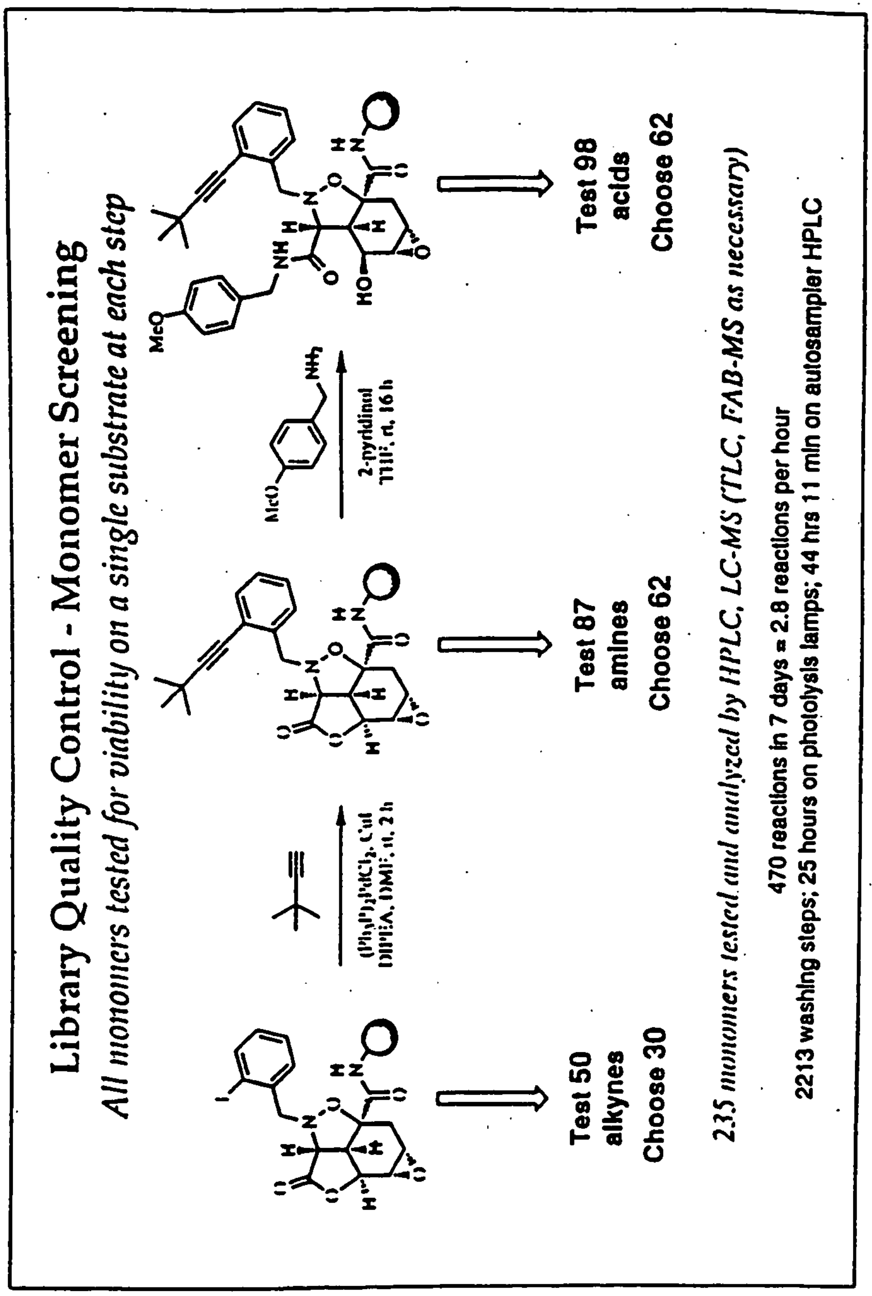

Library Quality Control - Monomer Screening
All monomers tested for viability on a single substrate at each step
(Ph3P)2PdCl2, CuI
DIPEA, DMF, rt, 2 h
2-pyridinol
THF, rt, 16 h
Test 50
alkynes
Choose 30
Test 87
amines
Choose 62
Test 98
acids
Choose 62
235 monomers tested and analyzed by HPLC, LC-MS (TLC, FAB-MS as necessary)
470 reactions in 7 days = 2.8 reactions per hour
2213 washing steps; 25 hours on photolysis lamps; 44 hrs 11 min on autosampler HPLC

Figure 42

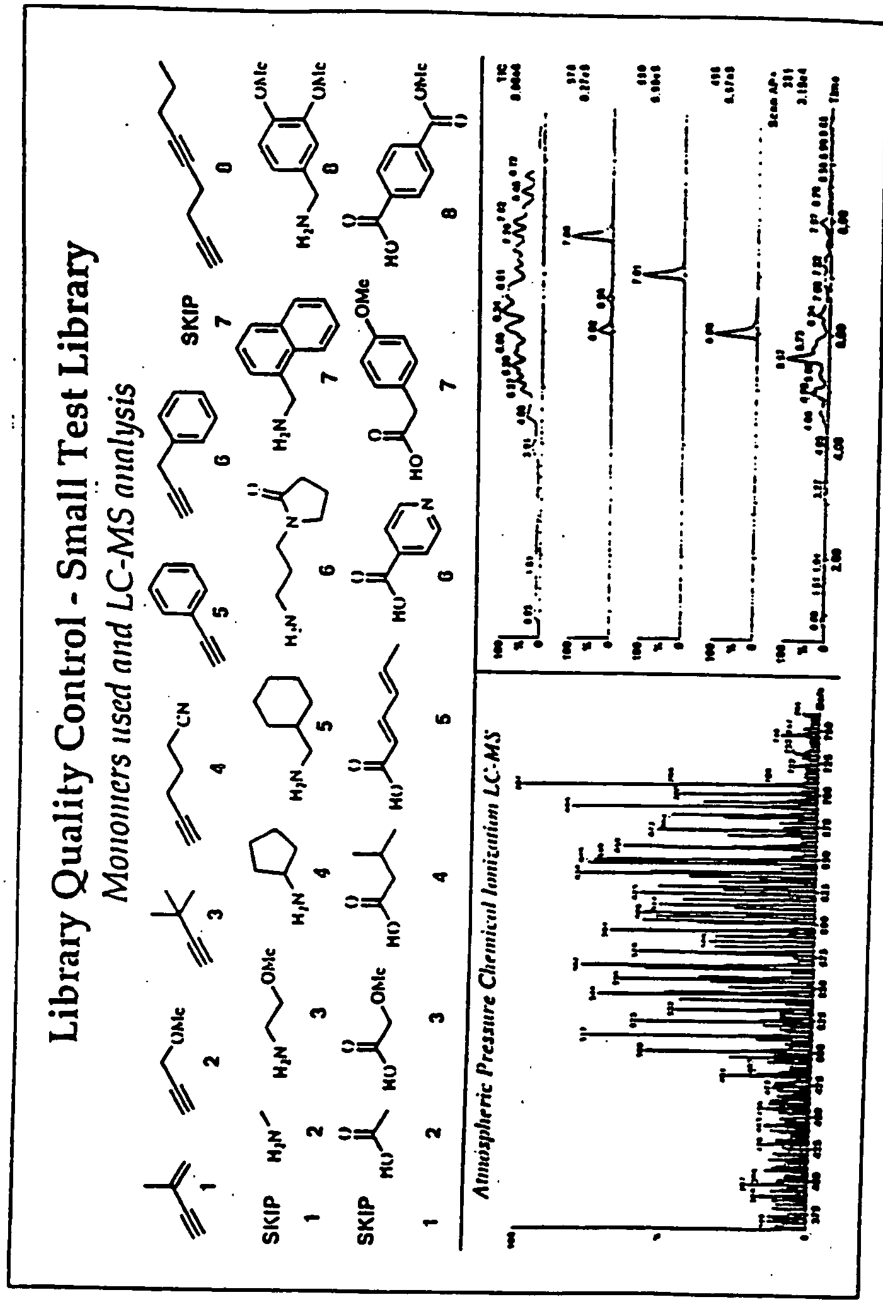

Library Quality Control - Small Test Library
Monomers used and LC-MS analysis
Atmospheric Pressure Chemical Ionization LC-MS
SKIP
SKIP
SKIP

Figure 43

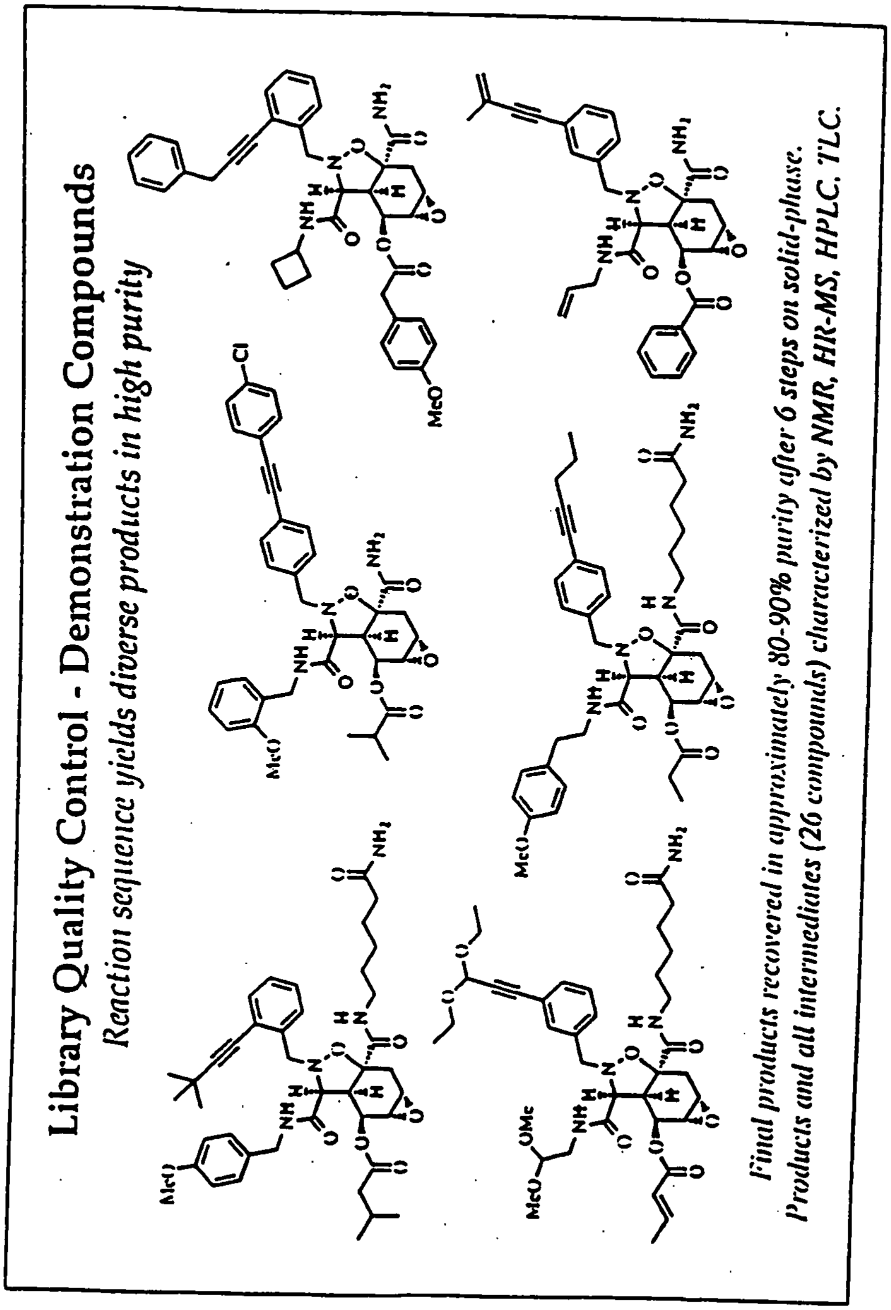

Library Quality Control - Demonstration Compounds
Reaction sequence yields diverse products in high purity
Final products recovered in approximately 80-90% purity after 6 steps on solid-phase.
Products and all intermediates (26 compounds) characterized by NMR, HR-MS, HPLC, TLC.

Figure 44

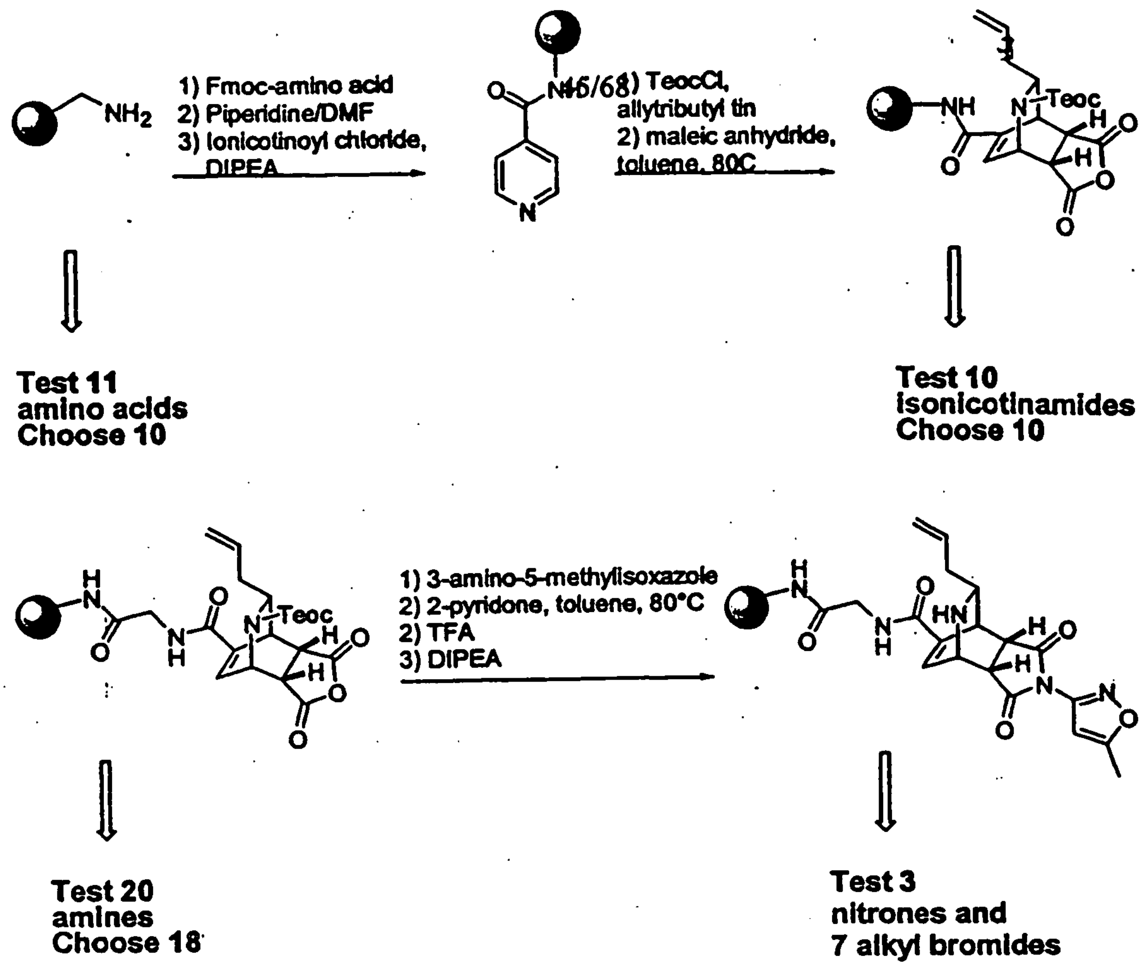

1) Fmoc-amino acid
2) Piperidine/DMF
3) Ionicotinoyl chloride, DIPEA
1) TeocCl, allytributyl tin
2) maleic anhydride, toluene, 80C
Test 11 amino acids Choose 10
Test 10 isonicotinamides Choose 10
1) 3-amino-5-methylisoxazole
2) 2-pyridone, toluene, 80°C
2) TFA
3) DIPEA
Test 20 amines Choose 18
Test 3 nitrones and 7 alkyl bromides

Figure 45

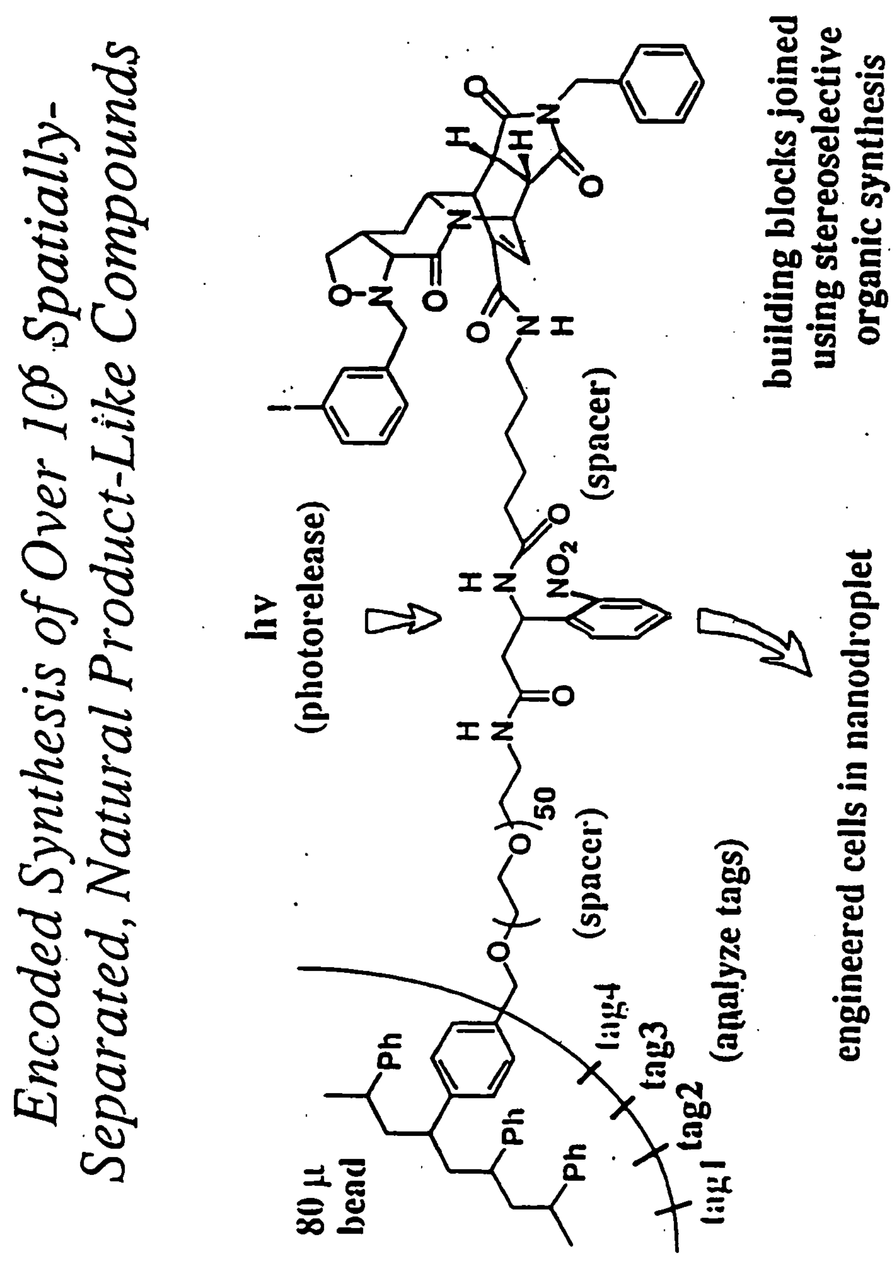

Encoded Synthesis of Over 10^6 Spatially-Separated, Natural Product-Like Compounds
80 µ bead
Ph
Ph
Ph
tag1
tag2
tag3
tag4
(analyze tags)
O
O
50
(spacer)
H
N
O
hv
(photorelease)
NO2
H
N
O
(spacer)
engineered cells in nanodroplet
H
N
O
O
N
O
N
O
H
H
N
O
I
building blocks joined
using stereoselective
organic synthesis

Figure 46

All 8 Pools of 64 Compounds in the Shikimic Acid Test Library Activate the 3TP Promoter, but KC 233 Prevents TGF-ß from Activating the 3TP Promoter

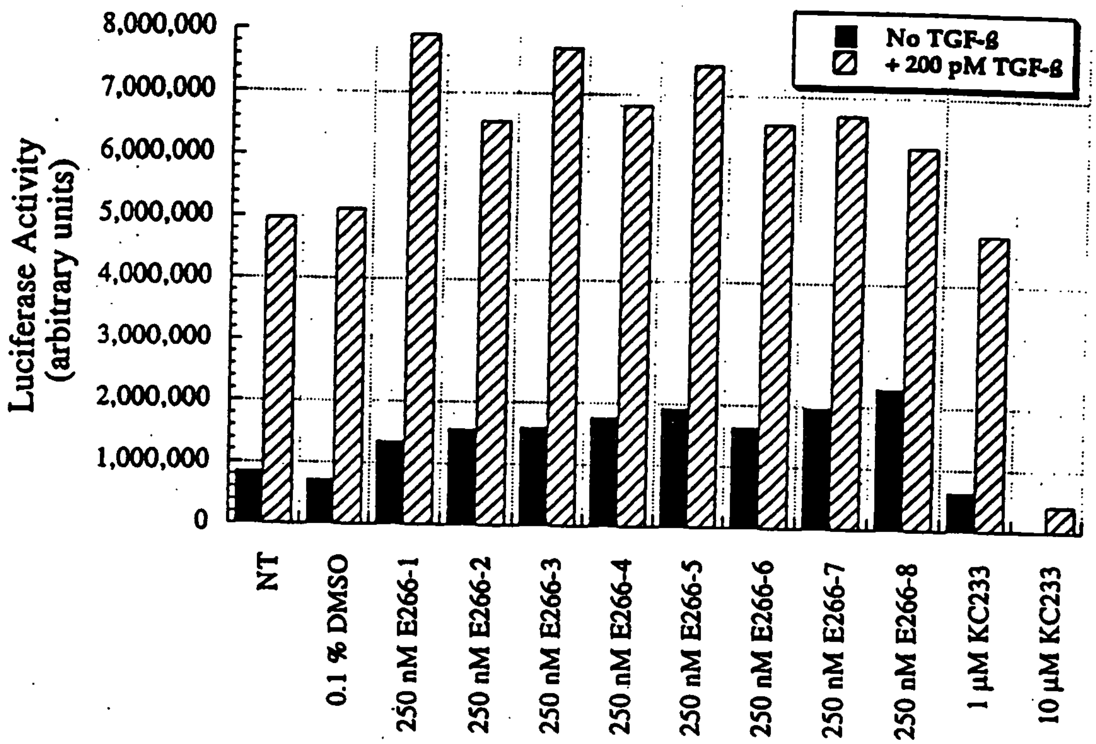


Figure 47

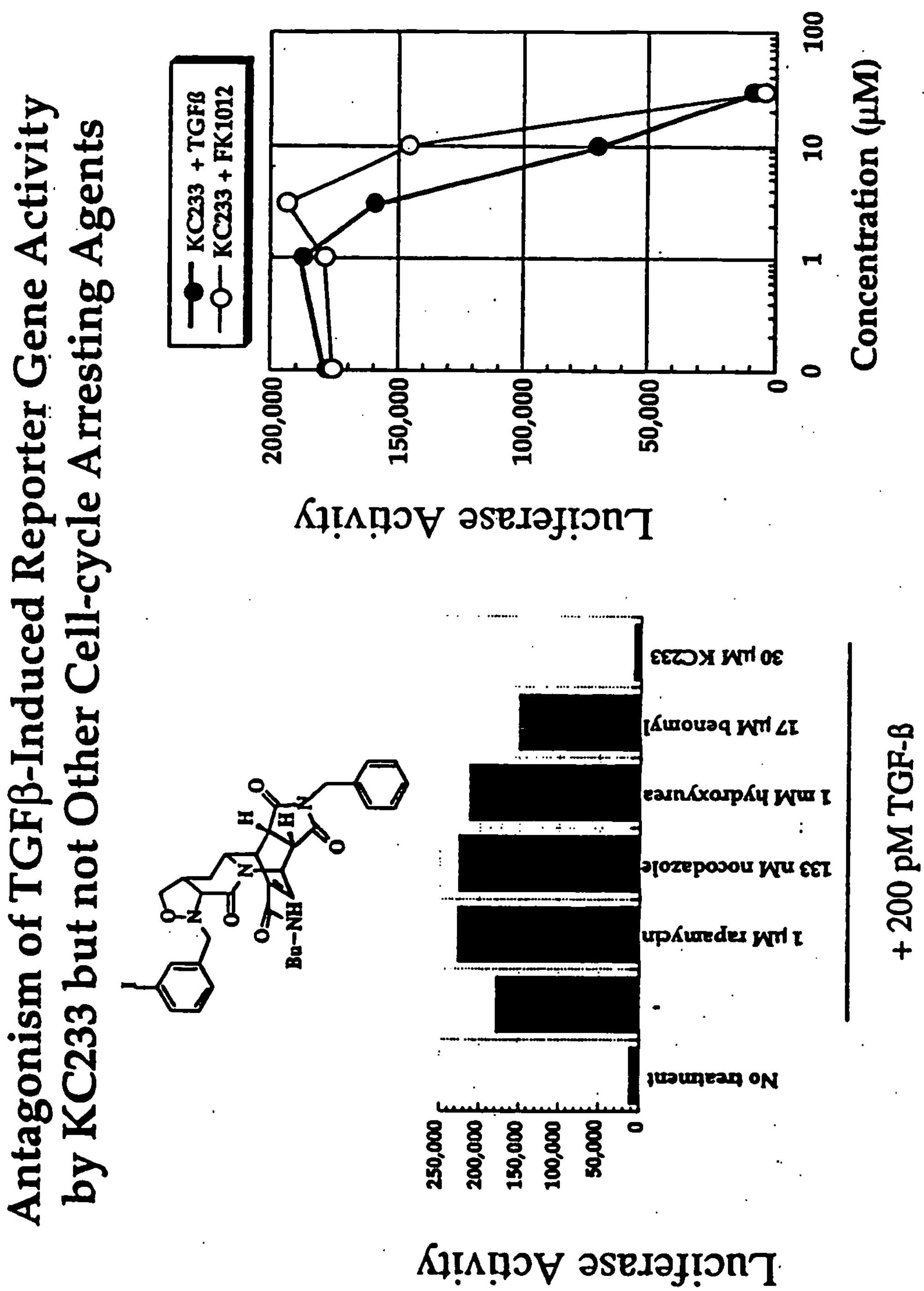

Antagonism of TGFβ-Induced Reporter Gene Activity
by KC233 but not Other Cell-cycle Arresting Agents
KC233 + TGFβ
KC233 + FK1012
Luciferase Activity
200,000
150,000
100,000
50,000
0
0
1
10
100
Concentration (µM)
O
N
H
Bu-NH
Luciferase Activity
250,000
200,000
150,000
100,000
50,000
0
No treatment
-
1 µM rapamycin
133 nM nocodazole
1 mM hydroxyurea
17 µM benomyl
30 µM KC233
+ 200 pM TGF-β

Figure 48

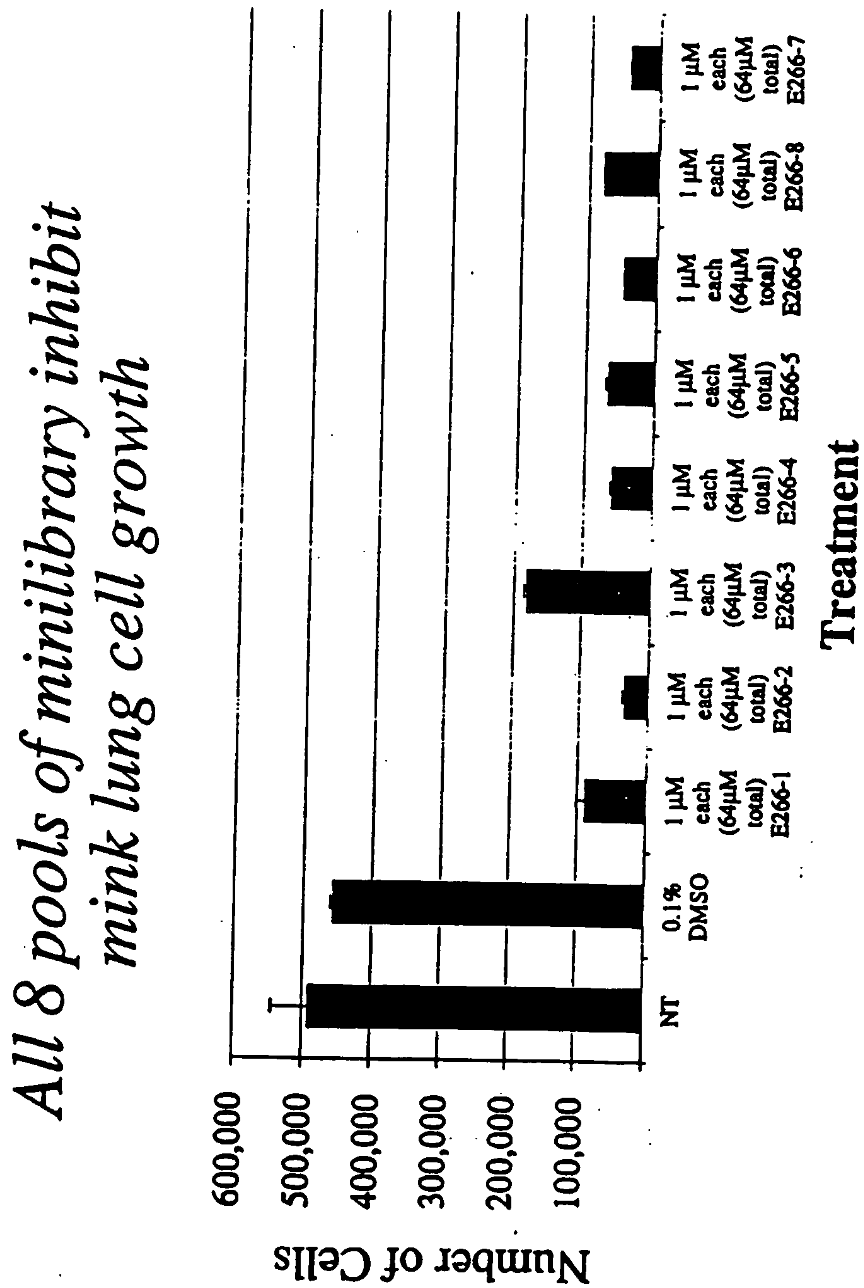

All 8 pools of minilibrary inhibit mink lung cell growth
Number of Cells
600,000
500,000
400,000
300,000
200,000
100,000
NT
0.1% DMSO
1 µM each (64µM total) E266-1
1 µM each (64µM total) E266-2
1 µM each (64µM total) E266-3
1 µM each (64µM total) E266-4
1 µM each (64µM total) E266-5
1 µM each (64µM total) E266-6
1 µM each (64µM total) E266-8
1 µM each (64µM total) E266-7
Treatment

Figure 49

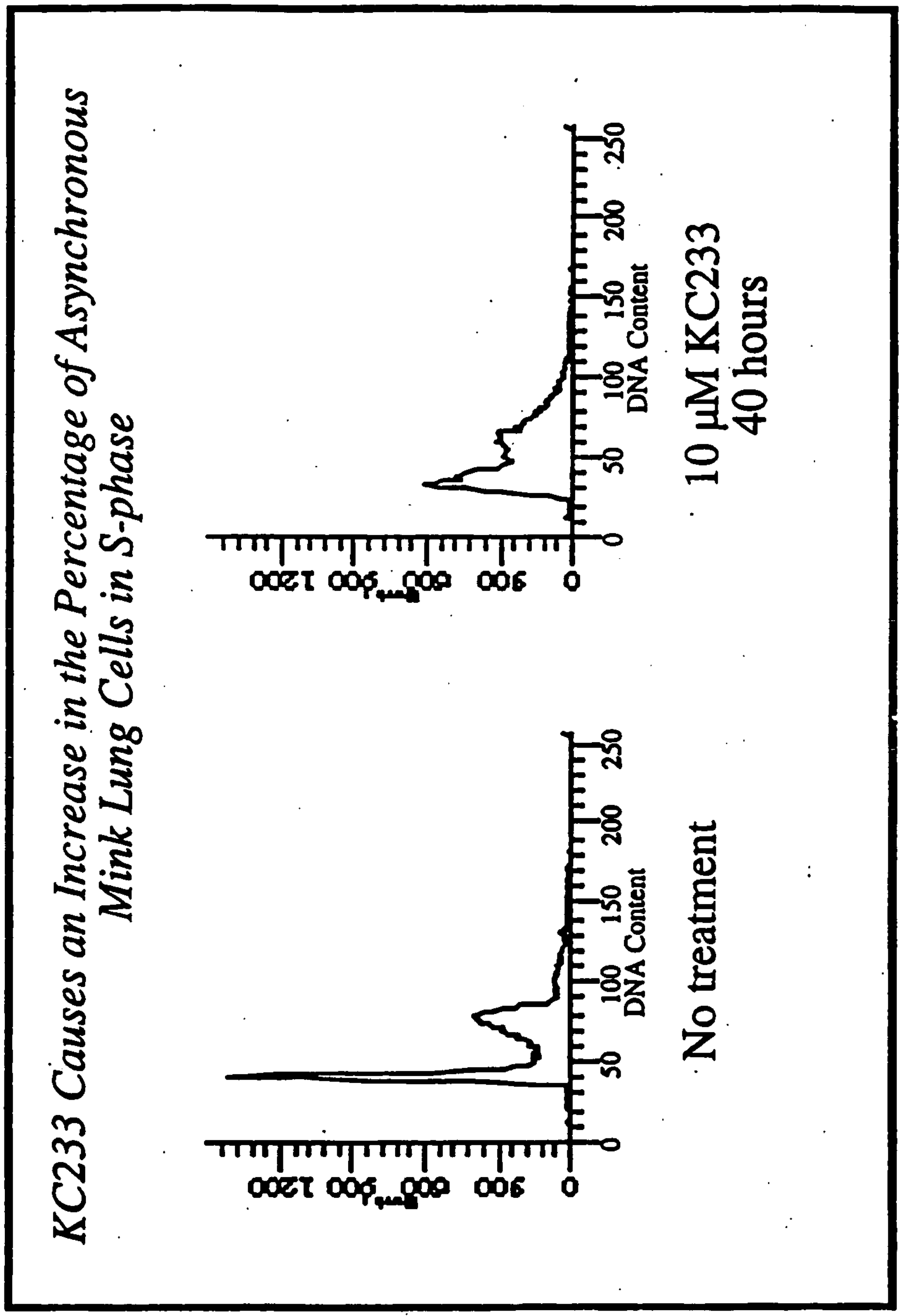
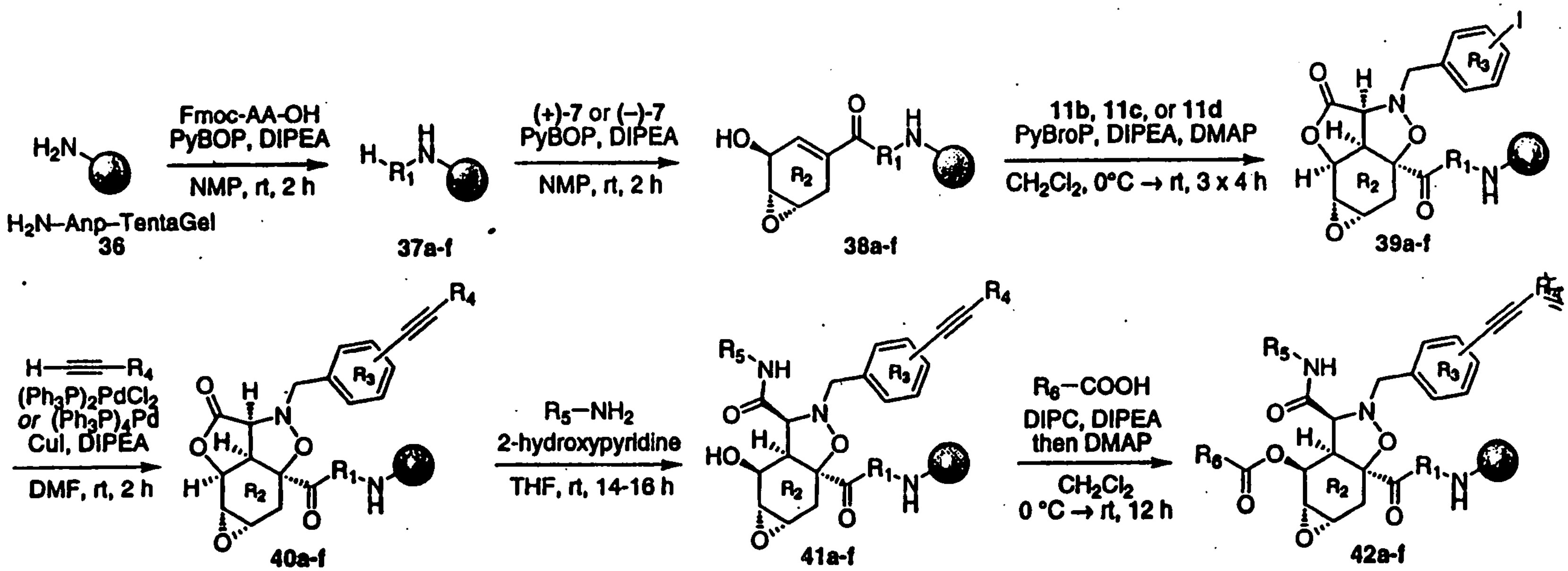
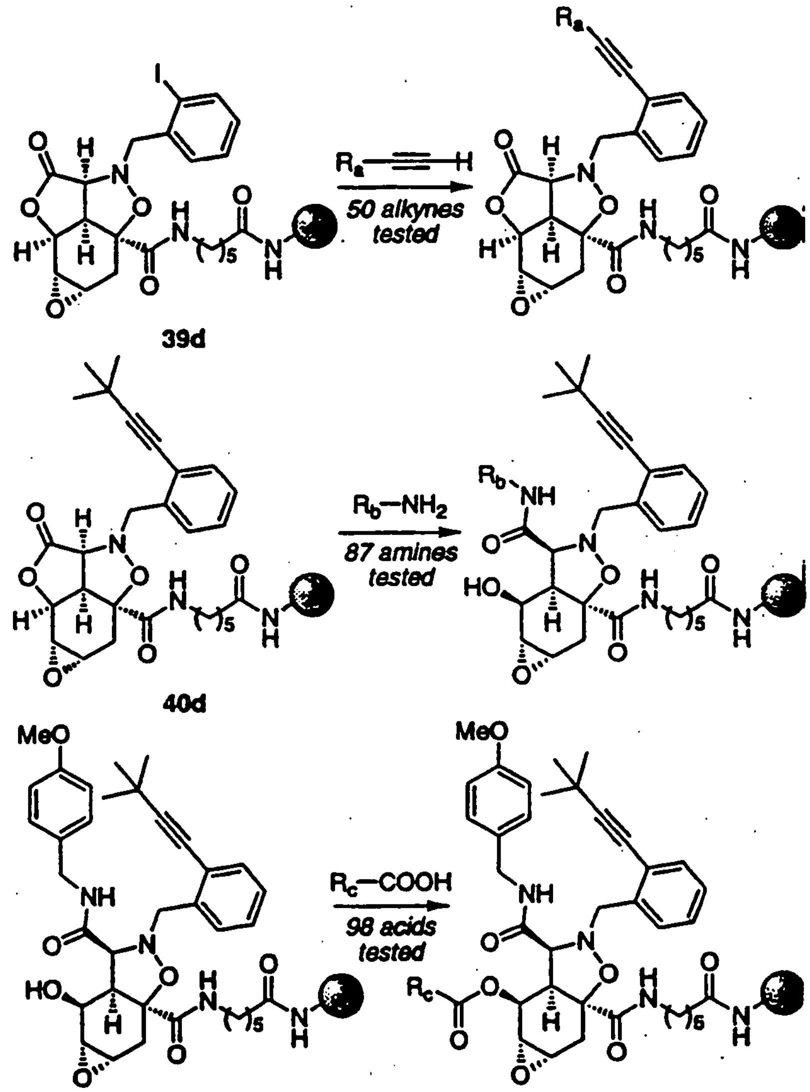

KC233 Causes an Increase in the Percentage of Asynchronous
Mink Lung Cells in S-phase
DNA Content
10 µM KC233
40 hours
DNA Content
No treatment

Figure 50



	R_1	R_2	R_3	R_4	R_5	R_6
a:	Ø	(+)-7	*ortho*	benzyl	cyclobutyl	4-methoxybenzyl
b:	Ø	(+)-7	*meta*	2-propenyl	allyl	phenyl
c:	Ø	(+)-7	*para*	4-chlorophenyl	2-methoxybenzyl	isopropyl
d:	Aca	(+)-7	*ortho*	*t*-butyl	4-methoxybenzyl	isobutyl
e:	Aca	(+)-7	*meta*	diethoxymethyl	2,2-dimethoxyethyl	1-propenyl
f:	Aca	(+)-7	*para*	propyl	4-methoxyphenethyl	ethyl

Figure 51

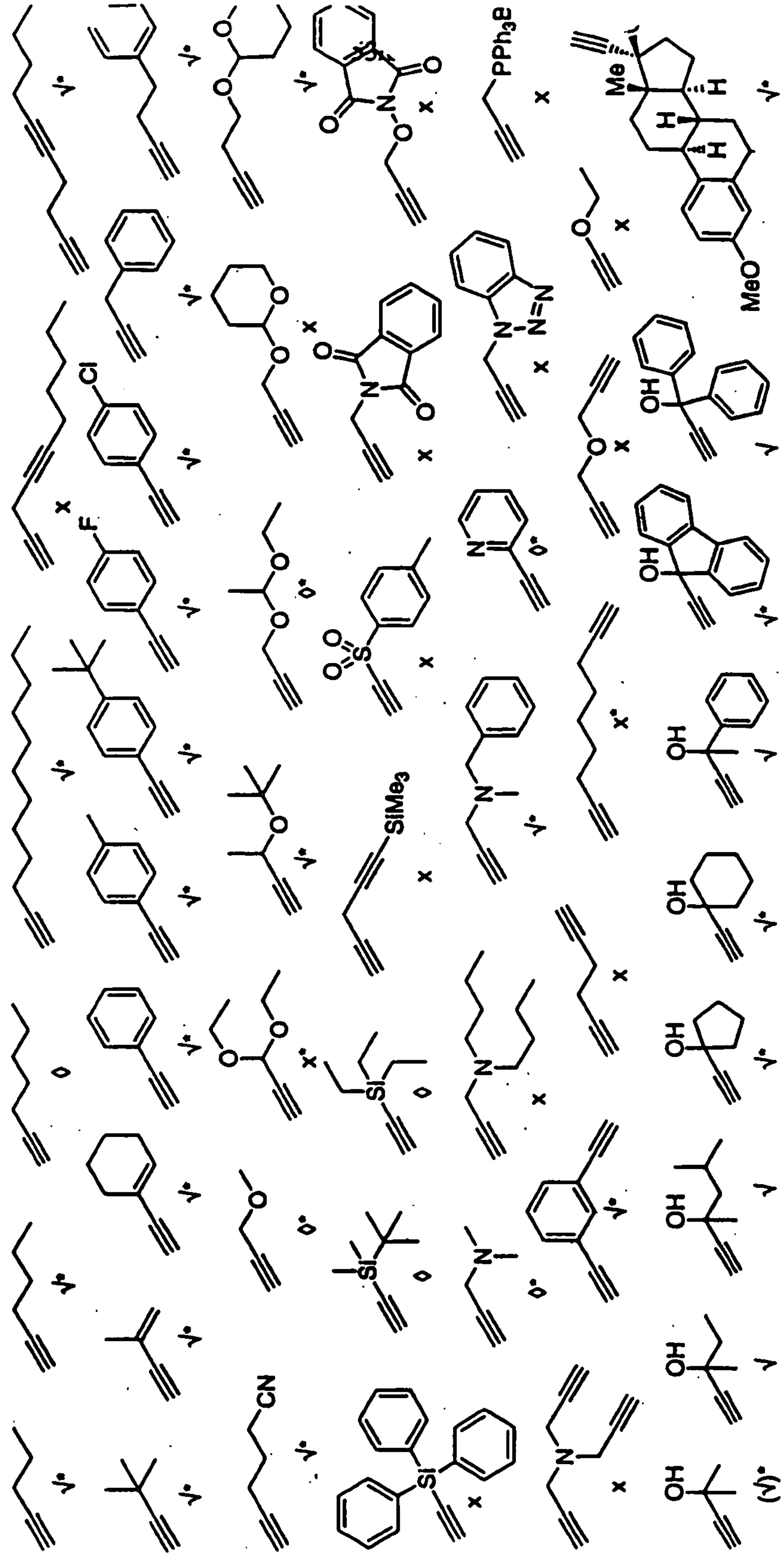


39d

40d

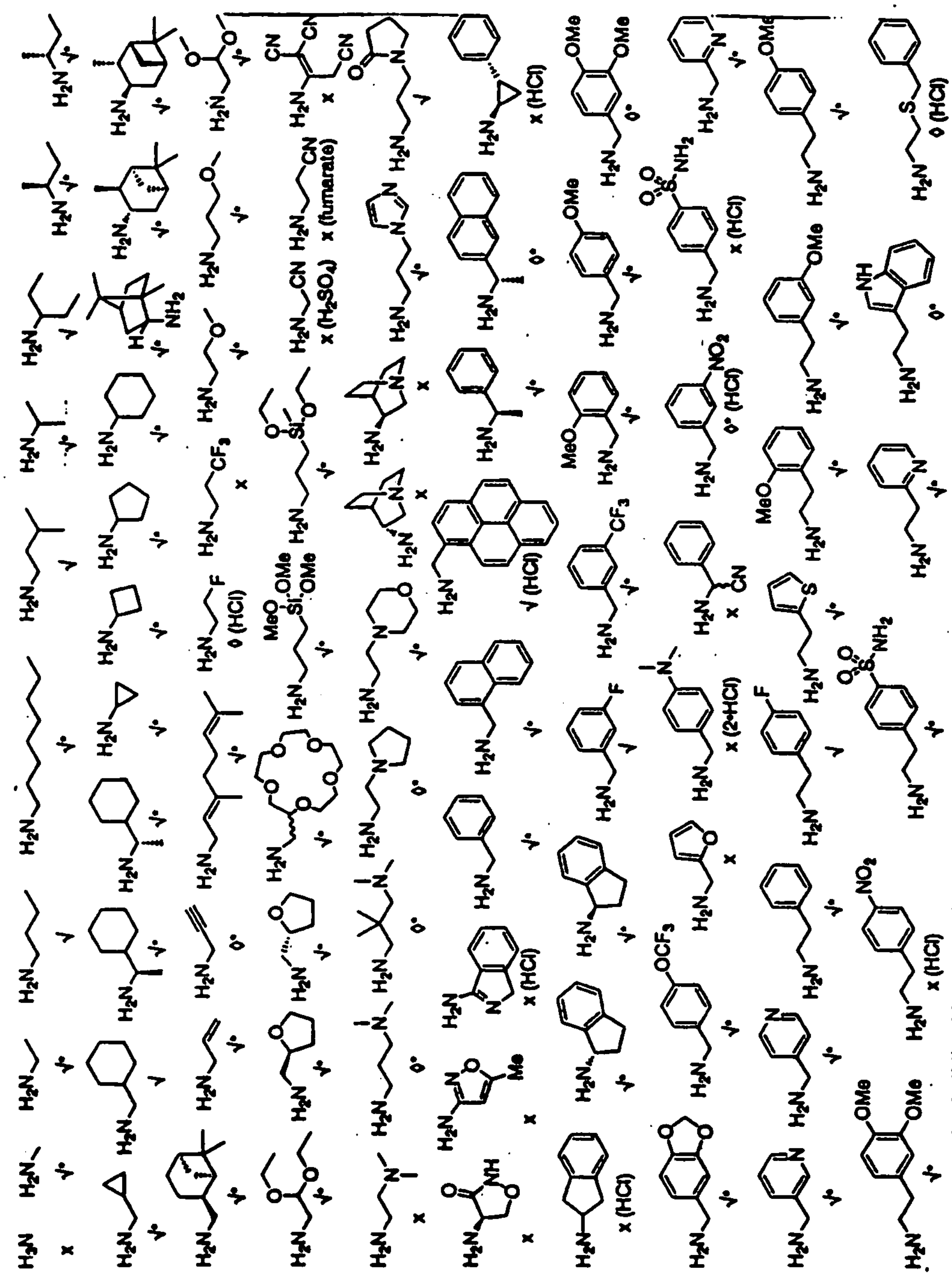
41d

Figure 52



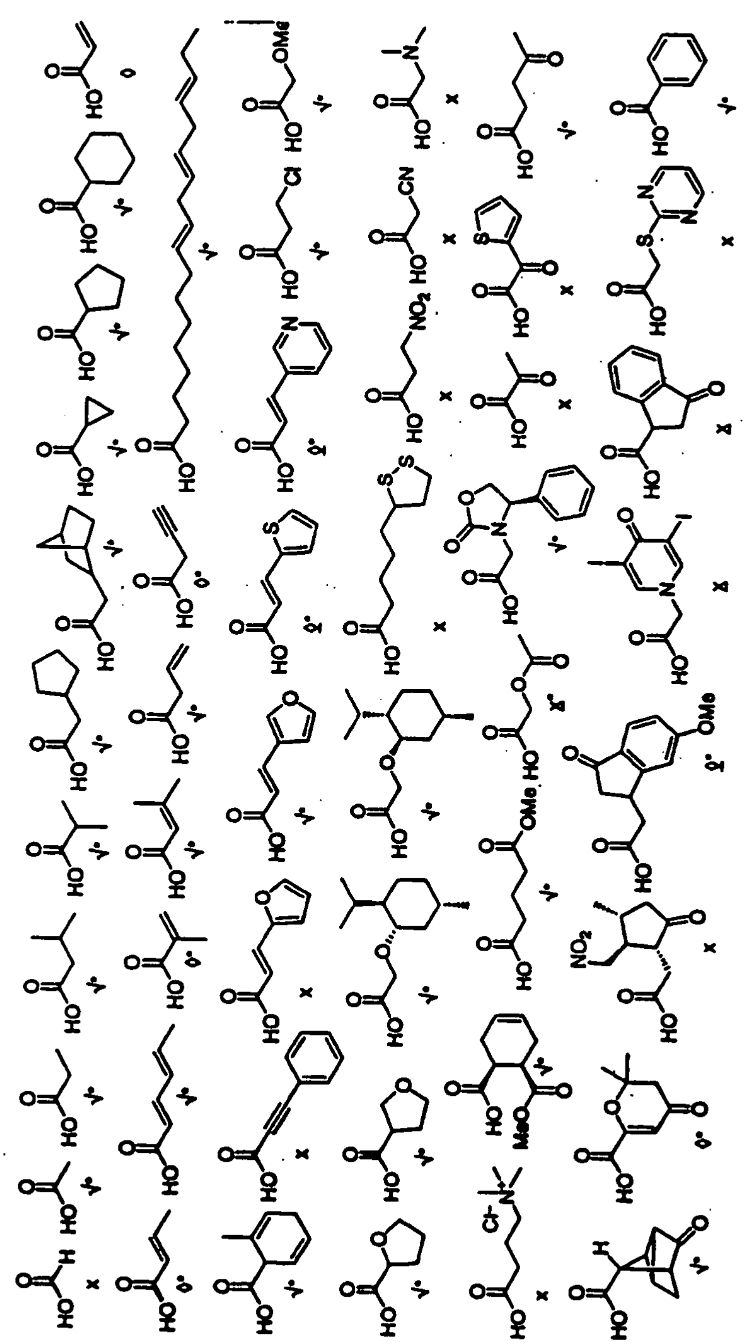
Alkyne building blocks tested in Sonogashira/Castro-Stephens reaction. Building blocks reacting with ≥80% conversion and purity are denoted by a √, 50-80% by a ◊, <50% by an x. Building blocks included in the full-scale library synthesis are denoted by a *.

Figure 53



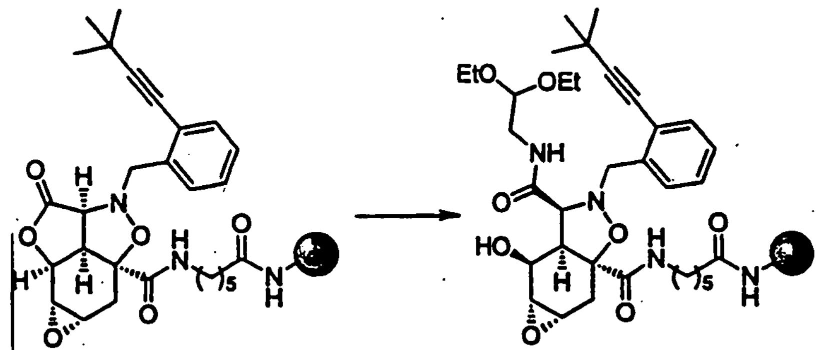
Amine building blocks tested in lactone aminolysis reaction. Salts indicated in parentheses were neutralized *in situ* with DIPEA. Building blocks reacting with ≥80% conversion and purity are denoted by a √, 50-80% by a 0, <50% by an X. Building blocks included in the full-scale library synthesis are denoted by a *.

Figure 54



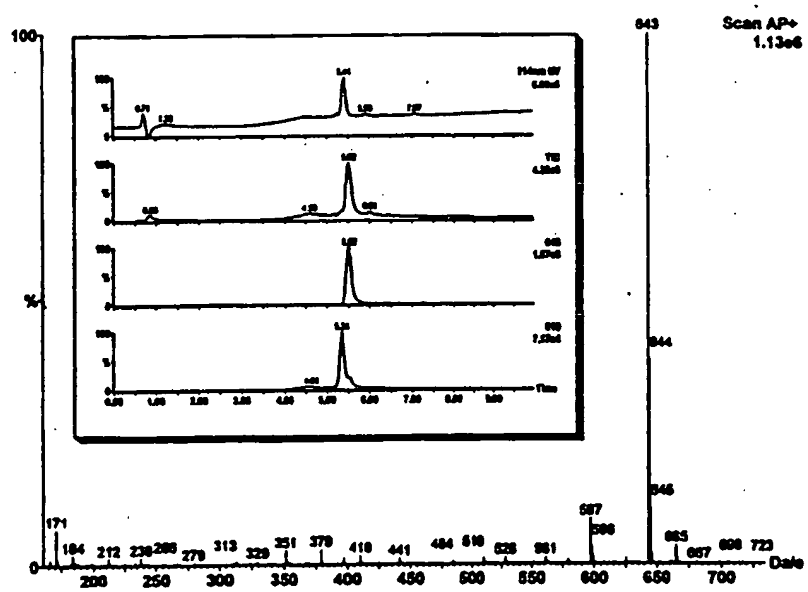
Carboxylic acid building blocks tested in acylation reaction. Building blocks reacting with ≥80% conversion and purity are denoted by a √, 50-80% by a 0, <50% by an x. Underlining indicates starting material 41d was of questionable purity. Building blocks included in the full-scale library synthesis are denoted by a *.

Figure 55

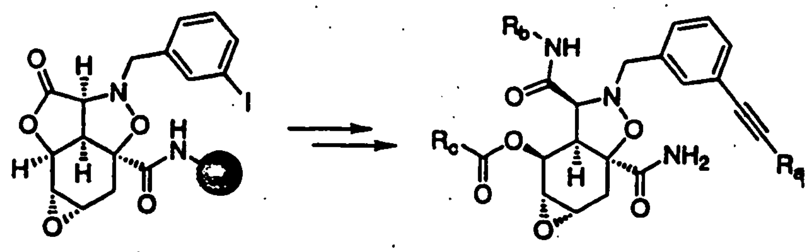


starting material, 40d
$[M+H]^+ = 510$

aminolysis product
$[M+H]^+ = 643$

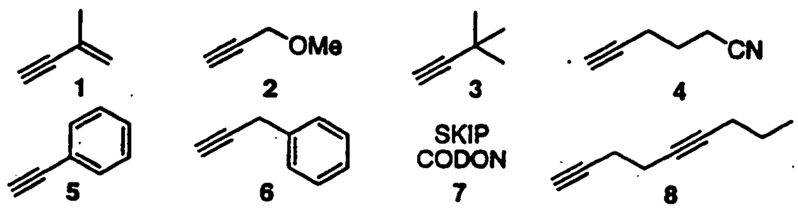


Representative LC-MS data for testing of building blocks. (*top*) Starting material and product structures. (*bottom*) Mass spectrum of product peak. (*inset*) 214 nm UV trace, Total Ion Count (TIC) trace, product mass trace, starting material mass trace. While the starting material is difficult to detect in the UV and TIC traces, a small amount is clearly seen in the single mass trace at 4% relative intensity compared to the product. Note the slight (0.09 min) delay between the UV detector and mass detector retention times.

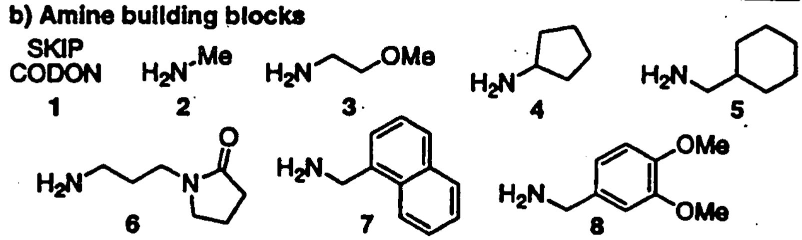


39b 43{R_a, R_b, R_c}

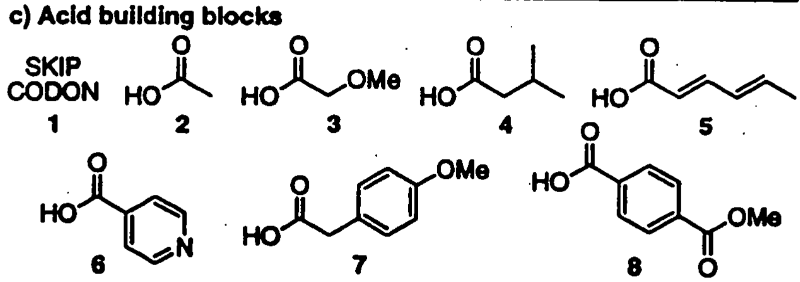
a) Alkyne building blocks



b) Amine building blocks



c) Acid building blocks



Tetracycle and building blocks used in test library.

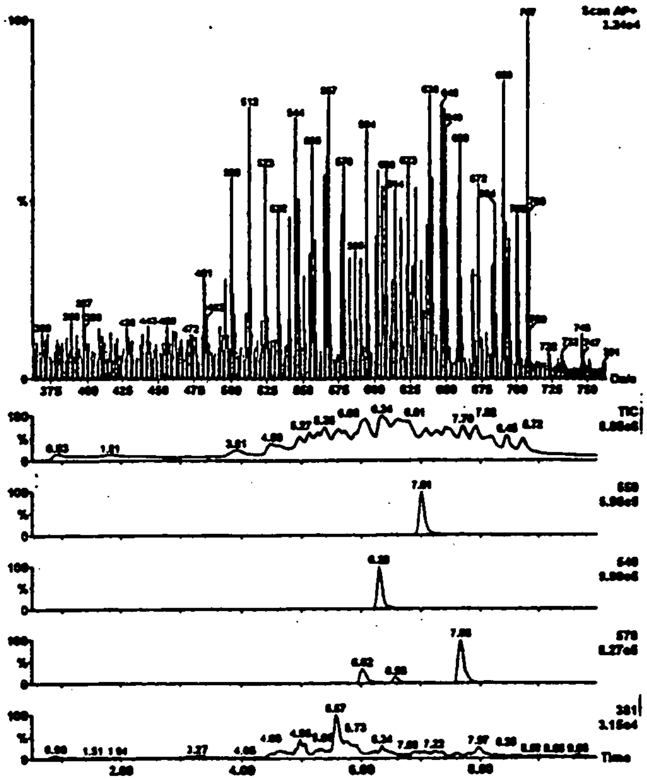
Figure 57

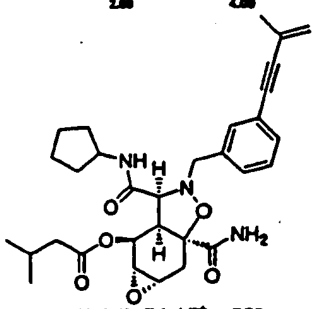
Amines

Alkynes		1	2	3	4	5	6	7	8
	MW	0	31	75	85	113	142	157	167
1	66	381	412	456	466	494	523	538	548
2	70	385	416	460	470	498	527	542	552
3	82	397	428	472	482	510	539	554	564
4	93	408	439	483	493	521	550	565	575
5	102	417	448	492	502	530	559	574	584
6	116	431	462	506	516	544	573	588	598
7	128	443	474	518	528	556	585	600	610
8	134	449	480	524	534	562	591	606	616

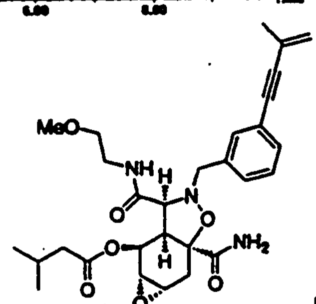
Alkyne and amine building block masses and the resulting 64 unique γ-hydroxyamide product masses. Acylation of the C-6 alcohol with a carboxylic acid shifts all of the product masses for that pool by the same value (mass of the acid minus water).

Figure 58

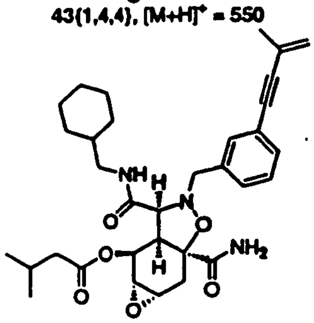




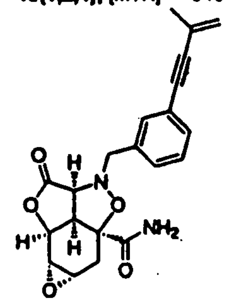
43{1,4,4}, $[M+H]^+ = 550$



43{1,2,4}, $[M+H]^+ = 540$



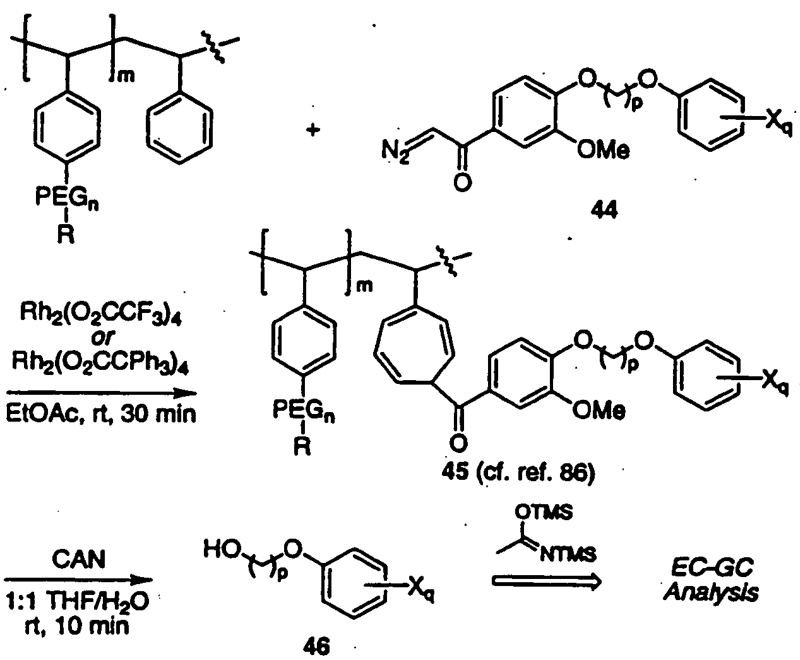
43{1,5,4}, $[M+H]^+ = 578$



43{1,1,(4)}, $[M+H]^+ = 381$

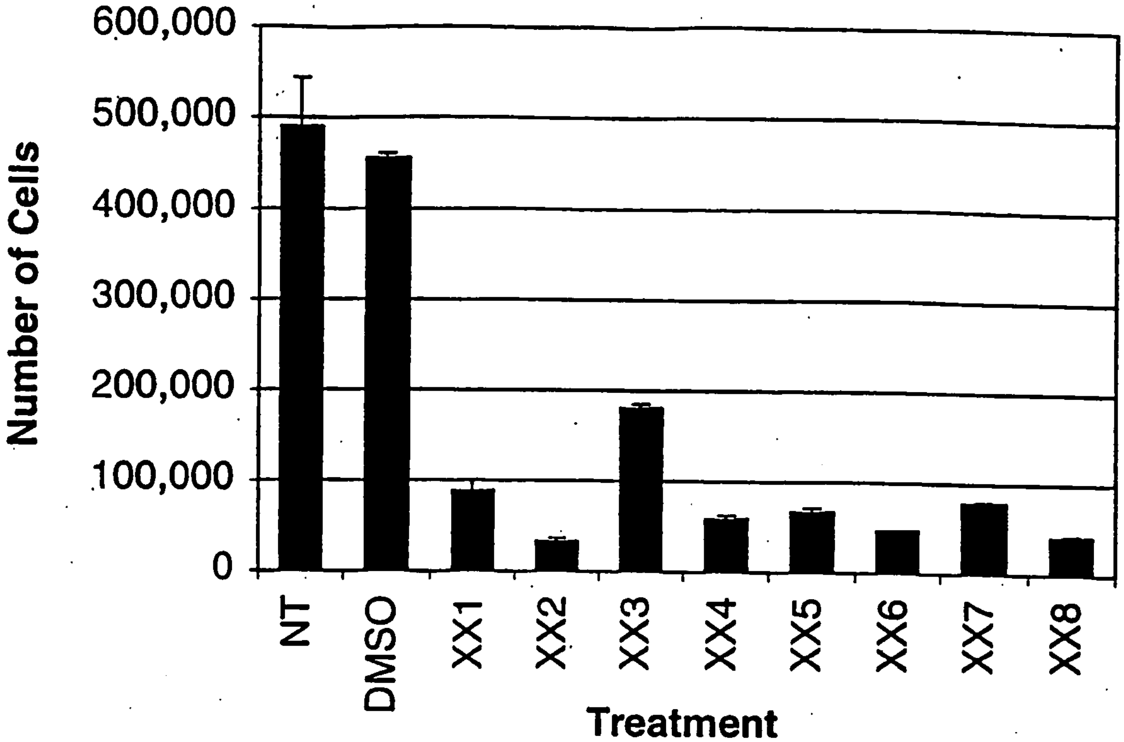
Representative LC-MS data for test library pool 43{X,X,4} acylated with Acid 4. (*top*) Mass spectrum averaged over entire chromatogram. (*middle*) TIC trace and single mass traces. (*bottom*) Corresponding structures. The 550 and 540 single mass traces represent typical "clean" product signals. Smaller peaks (6,02 min, 6.58 min) in the 578 single mass trace arise from isotopic compositions of lower mass products (FW = 575, 576). The 381 single mass trace is representative of a "weak" product signal.

Figure 59



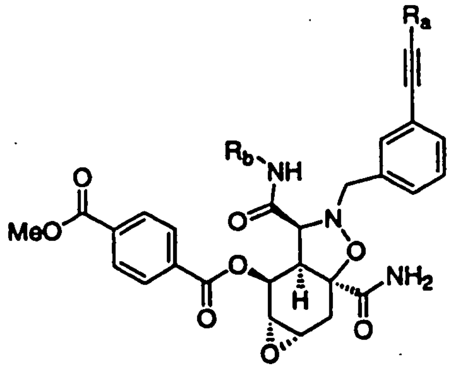
m
PEG$_n$
R
+
N_2
O
OMe
p
X_q
44
$Rh_2(O_2CCF_3)_4$
or
$Rh_2(O_2CCPh_3)_4$
EtOAc, rt, 30 min
45 (cf. ref. 86)
CAN
1:1 THF/H_2O
rt, 10 min
HO
46
OTMS
NTMS
EC-GC
Analysis

Figure 60

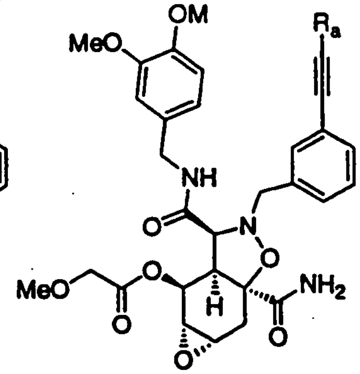


Mink lung cell proliferation assay. Lane 1: No treatment. Lane 2: 0.1% DMSO control. Lanes 3-10: Pools 43{X,X,1} through 43{X,X,8} at 1 mM concentration per compound. Data represent the average of three experiments with error bars indicating one SD.

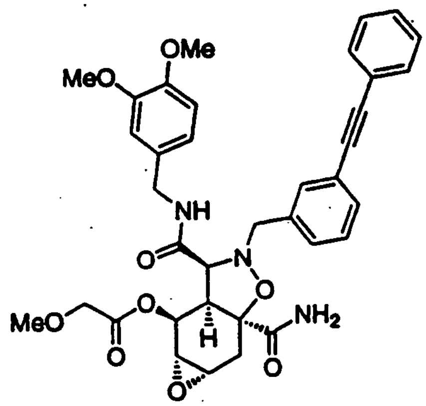
Figure 61



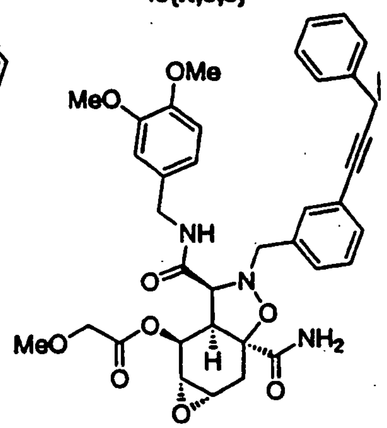
43{X,X,8}



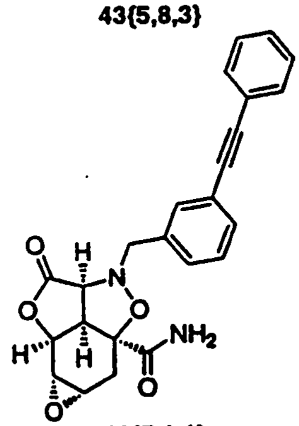
43{X,8,3}



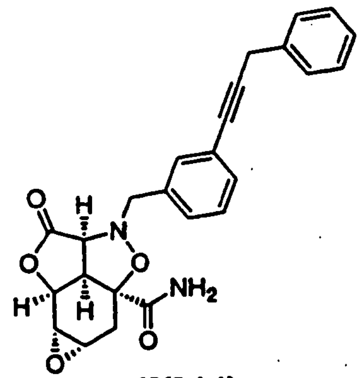
43{5,8,3}



43{6,8,3}



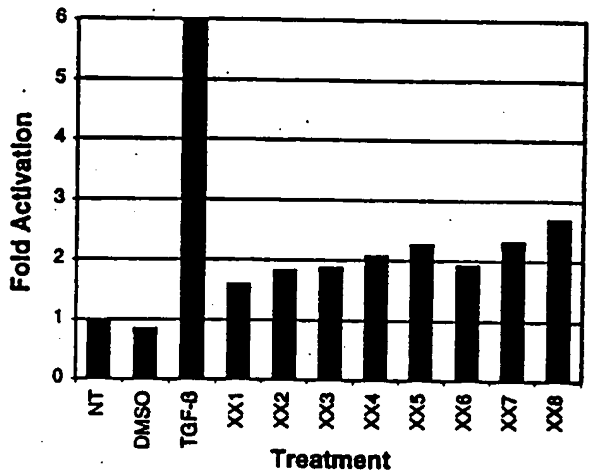
43{5,1,1}



43{6,1,1}

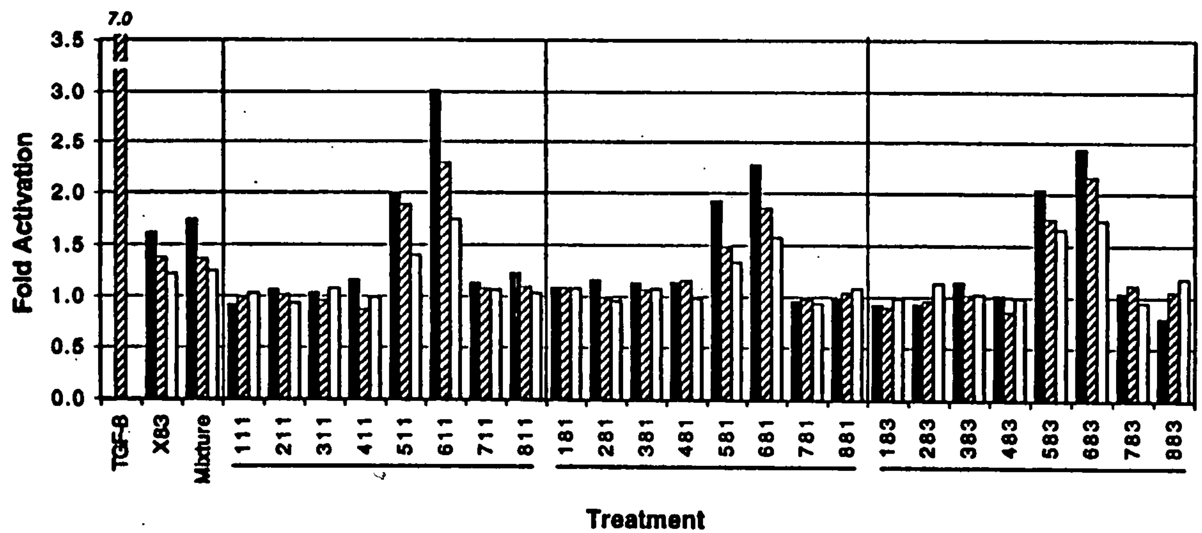
Activators of the TGF-β-responsive reporter gene.

Figure 62



TGF-β-responsive reporter gene assay. Lane 1: No treatment. Lane 2: 0.1% DMSO control. Lane 3: 200 pM TGF-β. Lanes 4-11: Pools 43{X,X,1} through 43{X,X,8} assayed at concentration of 250 nM per compound. Data represent a single experiment with fold activation calculated relative to untreated cells.

Figure 63



TGF-β-responsive reporter gene assay data. Lane 1: 1 nM TGF-β. Lanes 2 and 3: Pool 43{X,8,3} and mixture of individually synthesized compounds 43{1,8,3} through 43{8,8,3}, assayed at 2.5 (black bars), 1.25 (striped bars), and 0.625 μM (white bars) per compound. Lanes 4 27: Alkynylbenzyltetracycle precursors 43{1,1,1} through 43{8,1,1}, γ-hydroxyamide precursors 43{1,8,1} through 43{8,8,1}, and acylated final compounds 43{1,8,3} through 43{8,8,3}, assayed at 25, 12.5, and 6.25 μM per compound. Data represent average of two experiments with fold activation calculated relative to untreated cells (data not shown). Note that background signal from the instrument has not been subtracted.

Figure 64

Acid building blocks tested.

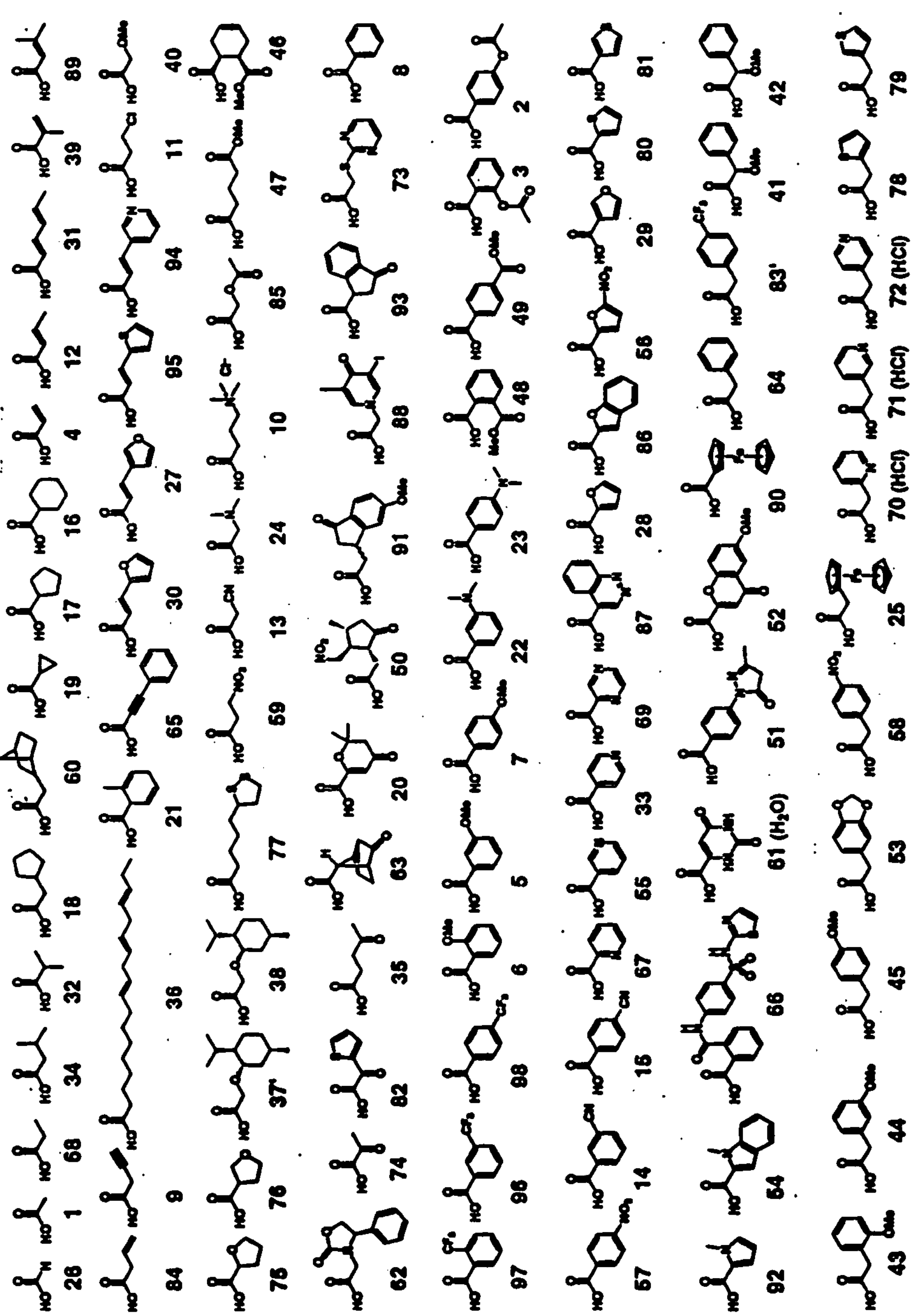


Figure 65

Amine building blocks tested.

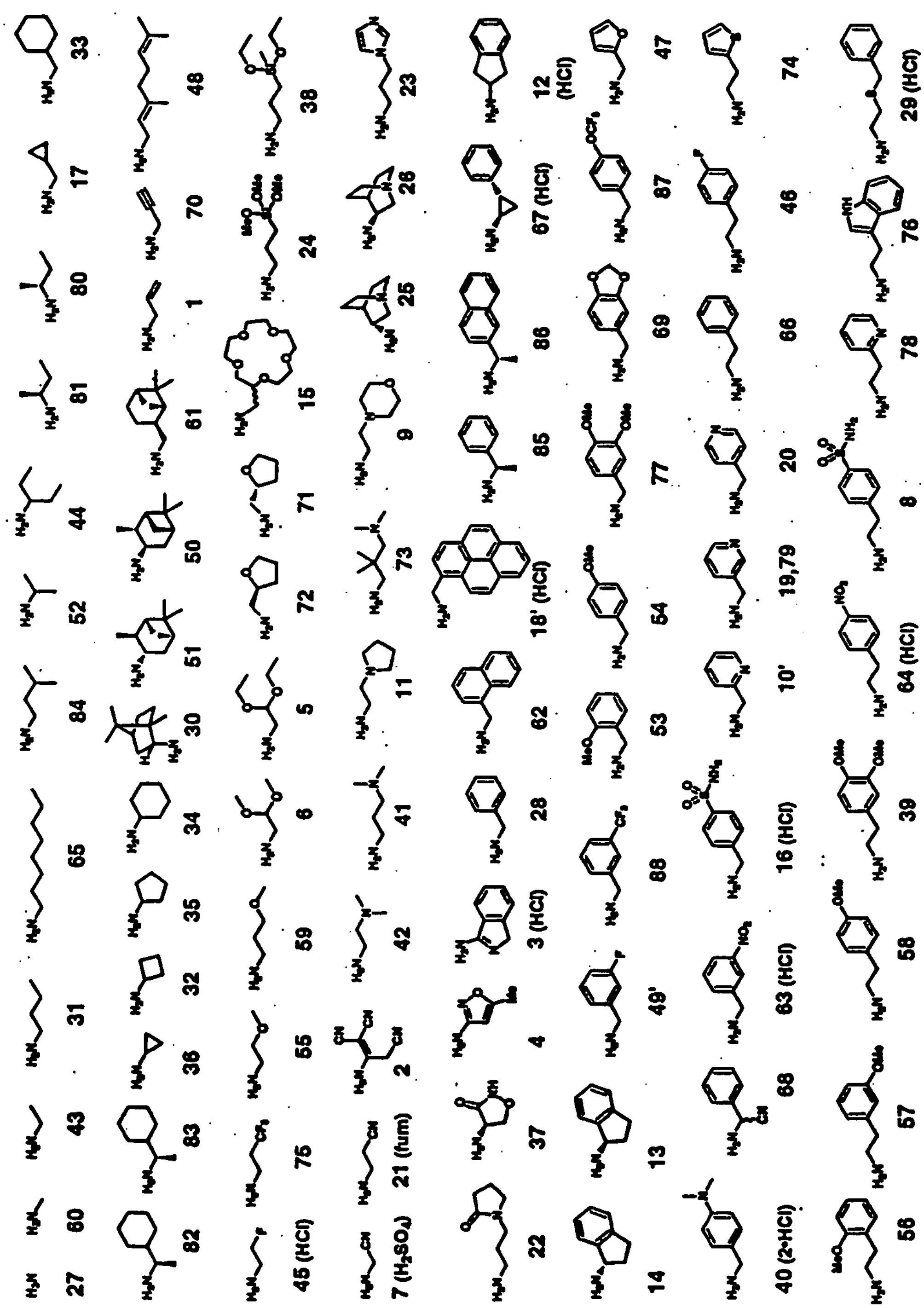


Figure 66

Alkyne building blocks tested.

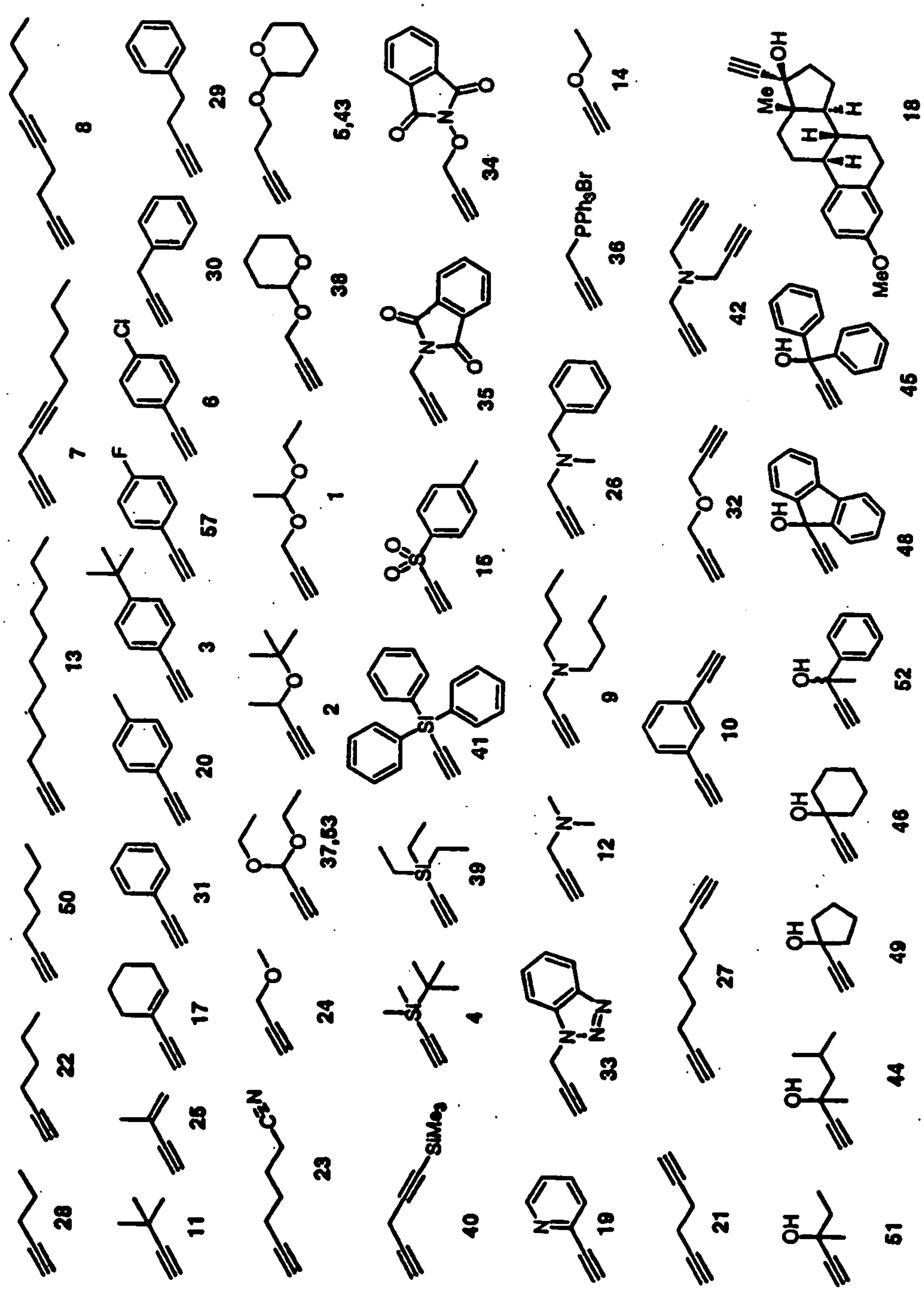
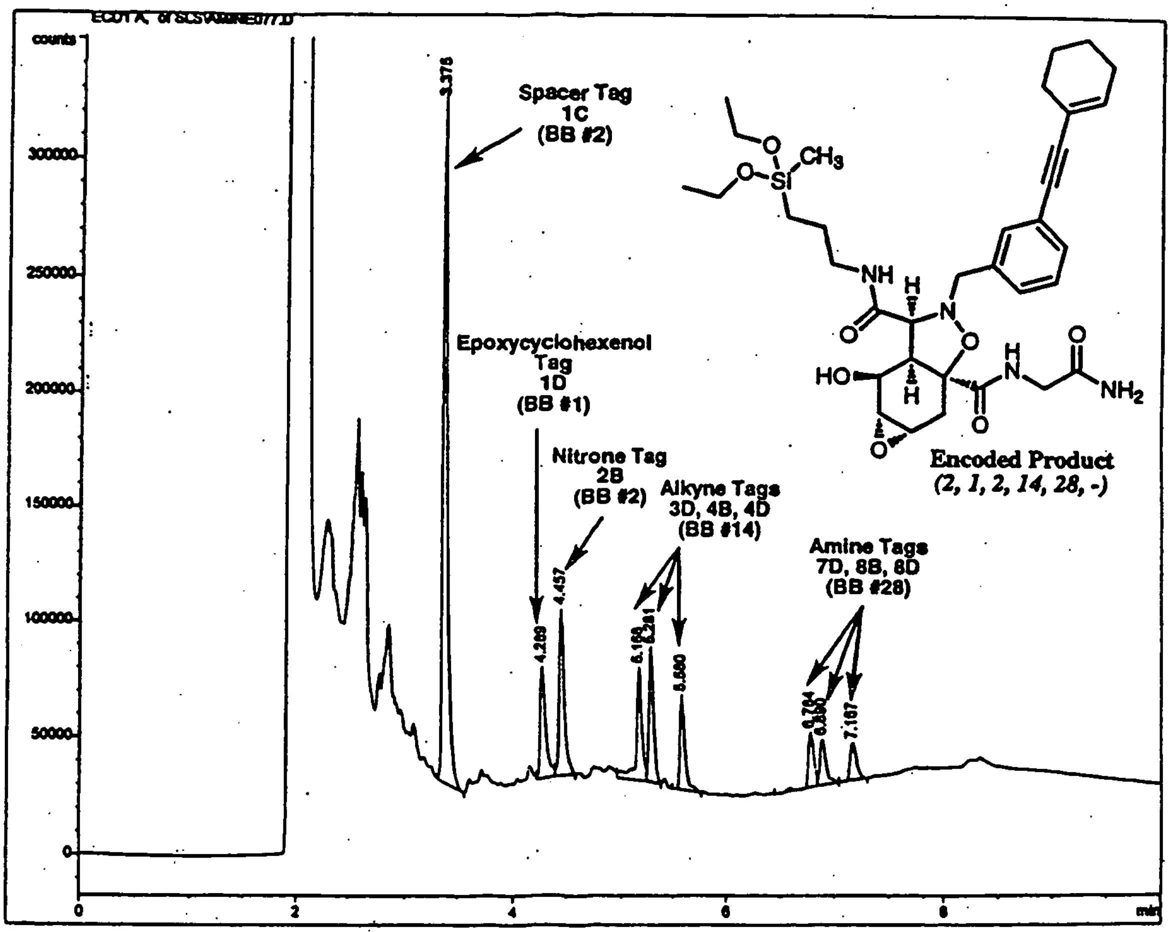


Figure 67



Representative EC-GC trace for binary encoding tag analysis. The sample analyzed was from the tag coupling reaction encoding amine building block 28. The product structure corresponding to the binary code is shown.

Figure 68

PCT

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International Bureau

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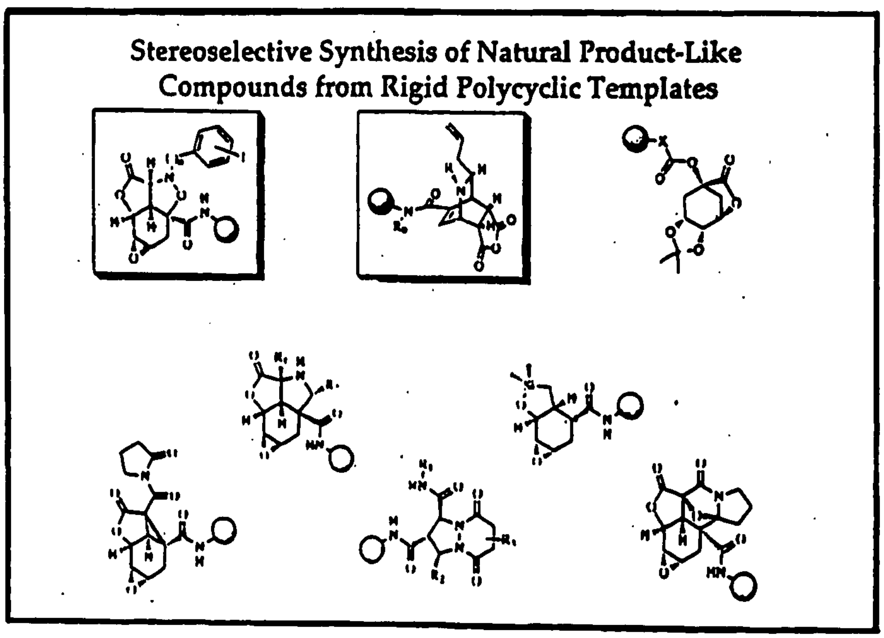
(54) Title: SYNTHESIS OF COMBINATORIAL LIBRARIES OF COMPOUNDS REMINISCENT OF NATURAL PRODUCTS

(57) Abstract

The present invention provides complex compounds reminiscent of natural products and libraries thereof, as well as methods for their production. The inventive compounds and libraries of compounds are reminiscent of natural products in that they contain one or more stereocenters, and a high density and diversity of functionality. In general, the inventive libraries are synthesized from diversifiable scaffold structures, which are synthesized from readily available or easily synthesizable template structures. In certain embodiments, the inventive compounds and libraries are generated from diversifiable scaffolds synthesized from a shikimic acid based epoxyol template. In other embodiments, the inventive compounds and libraries are generated from diversifiable scaffolds synthesized from the pyridine-based template isonicotinamide. The present invention also provides a n vel ortho-nitrobenzyl photolinker and a method for its synthesis. Furthermore, the present invention provides methods and kits for determining one or more biol gical activities f members of the inventive libraries. Additionally, the present invention provides pharmaceutical compositions containing one or more library members.



*(Referred to in PCT Gazette No. 16/2000, Section II)

(Continued)
237/20, 237/24, 247/14, C07D 205/00, 261/00, 261/20, 303/46, 307/83, 471/08, 471/16, 471/18, 471/22, 491/18, 491/22, 493/06, 495/18, 495/22, 498/06, 498/16, 498/22, G01N 33/53

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07B61/00 C07C227/10 C07C231/12 C07C235/40 C07C237/20
C07C237/24 C07C247/14 C07D205/00 C07D261/00 C07D261/20
C07D303/46 C07D307/83 C07D471/08 C07D471/16 C07D471/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07B C07C C07D G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 16830 A (HARVARD COLLEGE) 23 April 1998 (1998-04-23) page 2 -page 3 claim 25 figures 7-10 ---	1-7, 11-19, 46-50, 115,116
A	HUFF R.K. ET AL.: "The Nonadrides. Part VI. Dimerisation of the C9 unit in vivo and in vitro" J. CHEM. SOC.,1972, pages 2584-2590, XP002136145 ---	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	28. 07. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Held, P

International Application No
PC.,US 99/16753

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/22 C07D491/18 C07D491/22 C07D493/06 C07D495/18
C07D495/22 C07D498/06 C07D498/16 C07D498/22 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TAN, DEREK S. ET AL: "Stereoselective Synthesis of over Two Million Compounds Having Structural Features Both Reminiscent of Natural Products and Compatible with Miniaturized Cell-Based Assays" J. AM. CHEM. SOC. (1998), 120(33), 8565-8566, XP002136146 the whole document -----	1-7, 11-19, 46-50, 115,116

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Held, P

International application No.
PCT/US 99/16753

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7(part),11-14, 15-19(part),45-50, 115(part),116 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATI N CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-7 (partially), 11-14, 15-19 (partially), 46-50, 115 (partially), 116 (partially)

Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of formula 11(a) and 11(b), library made of those template compounds, screening method and kit.

2. Claims: 1-7 (partially), 15-19 (partially), 20 (partially), 25-27, 103-106, 115 (partially), 116 (partially)

Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 25 (a) and (b), library made of those template compounds, screening method and kit.

3. Claims: 1-7 (partially), 15-24 (partially), 99-102, 115 (partially), 116 (partially)

Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formula found in claim 22 and not covered by claim 25, library made of those template compounds, screening method and kit.

4. Claims: 1-7 (partially), 15-21 (partially), 23 (partially), 24 (partially), 95-98, 115 (partially), 116 (partially)

Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formula found in claim 21 and not covered by claims 22 or 25, library made of those template compounds, screening method and kit.

5. Claims: 1-7 (partially), 15-20 (partially), 23 (partially), 24 (partially), 91-94, 115 (partially), 116 (partially)

Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 20 (a) and (b) and not covered by claims 21, 22 or 25, library made of those template compounds, screening method and kit.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 1-7 (partially), 28 (partially), 29, 30-32 (partially), 87-90, 115 (partially), 116 (partially)

   Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 29, library made of those template compounds, screening method and kit.

7. Claims: 1-7 (partially), 28 (partially), 30-32 (partially), 79-82, 115 (partially), 116 (partially)

   Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 28 and not covered by claim 29, library made of those template compounds, screening method and kit.

8. Claims: 1-7 (partially), 33 (partially), 34, 35-37 (partially)

   Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 34.

9. Claims: 1-7 (partially), 33 (partially), 35-37 (partially), 83-86, 115 (partially), 116 (partially)

   Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 33 and not covered by claim 34, libraries made of those template compounds, screening method and kit.

10. Claims: 1-7 (partially), 38-41, 107-110, 115 (partially), 116 (partially)

    Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 38, libraries made of those template compounds, screening method and kit.

11. Claims: 1-7 (partially), 42-45, 111-114, 115 (partially), 116 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method for generating one or more isolated complex compounds reminiscent of natural products comprising synthesizing templates of the formulas found in claim 42, libraries made of those template compounds, screening method and kit.

12. Claims: 1-7 (partially), 15-19 (partially), 51-54, 115 (partially), 116 (partially)

Library of isolated complex compounds comprising the structure found in claim 51, the compounds per se, screening method and kit.

13. Claims: 1-7 (partially), 15-19 (partially), 55-58, 115 (partially), 116 (partially)

Library of isolated complex compounds comprising the structure found in claim 55, the compounds per se, screening method and kit.

14. Claims: 1-7 (partially), 15-19 (partially), 59-62, 115 (partially), 116 (partially)

Library of isolated complex compounds comprising the structure found in claim 59, the compounds per se, screening method and kit.

15. Claims: 1-7 (partially), 15-19 (partially), 63-66, 115 (partially), 116 (partially)

Library of isolated complex compounds comprising the structure found in claim 63, the compounds per se, screening method and kit.

16. Claims: 1-7 (partially), 15-19 (partially), 67-70, 115 (partially), 116 (partially)

Library of isolated complex compounds comprising the structure found in claim 67, the compounds per se, screening method and kit.

17. Claims: 1-7 (partially), 15-19 (partially), 71-74, 115 (partially), 116 (partially)

FURTHER INFORMATION C NTINUED FROM PCT/ISA/ 210

Library of isolated complex compounds comprising the structure found in claim 71, the compounds per se, screening method and kit.

18. Claims: 1-7 (partially), 15-19 (partially), 75-78, 115 (partially), 116 (partially)

Library of isolated complex compounds comprising the structure found in claim 75, the compounds per se, screening method and kit.

19. Claims: 15-19 (partially), 115 (partially), 116 (partially)

Method for generating a library of isolated complex compounds reminiscent of natural products comprising the synthesis of epoxyol templates and not covered by former subjects, screening method and kit.

20. Claims: 1-7 (partially), 115 (partially), 116 (partially)

Method for generating a library of isolated complex compounds reminiscent of natural products not covered by former subjects, screening method and kit.

21. Claims: 8-10

Method for generating a novel ortho-nitrobenzyl photolabile linker

INTERNATIONAL SEARCH REPORT

rmation on patent family members

Internat‸onal Application No
PC., US 99/16753

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9816830 A	23-04-1998	AU 5239198 A	11-05-1998